LABORATORY DIAGNOSTIC ASPECTS OF URINARY TRACT INFECTION – POTENTIAL IMPACT ON ANTIMICROBIAL STEWARDSHIP

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Disclosure

None
OBJECTIVES

1. Describe pre-analytical laboratory strategies for the diagnosis of UTI that support antimicrobial stewardship
2. Describe analytical laboratory strategies for the diagnosis of UTI that support antimicrobial stewardship
3. Describe post-analytical laboratory strategies for the diagnosis of UTI that support antimicrobial stewardship
INTRODUCTION

- UTI - common reason for seeking medical care; 50% of females ≥ 1 UTI in life
- 8 million office visits/year; 1 million hospital admissions
- 7 million cases of cystitis; 250K of pyelo
- UTI – cystitis, pyelonephritis, urethritis
  - Bacteriuria – symptomatic vs asymptomatic
  - Complicated vs uncomplicated (normal UT)
CLINICAL MANIFESTATIONS

- Infants - failure to thrive, vomiting, fever, non-specific
- Children - frequency, urgency, dysuria, flank or abdominal pain
- Adults (cystitis) - frequency, urgency, dysuria, turbid urine, suprapubic heaviness or pain, hematuria, pyuria
CLINICAL MANIFESTATIONS

- Adults (pyelonephritis) - fever, chills, flank pain, frequency, urgency, dysuria, pyuria
- Elderly – problematic; may be asymptomatic, pyuria may be absent, typical symptoms may occur; mortality from bacteremic UTI 10-30%
ETIOLOGY

- Uncomplicated - *E. coli* (75-90%), others - *S. saprophyticus* (5-15%), *Klebsiella, Proteus, Enterococcus, Pseudomonas*

- Complicated/HAI - *E. coli* (50%), other *Enterobacteriaceae, Pseudomonas, Acinetobacter, Enterococcus, staphylococci*
ETIOLOGY

- Elderly (males) - *Proteus = Providencia, E. coli, Pseudomonas;* (females) - *E. coli,* *Proteus,* *Klebsiella*

- Anaerobes - rare; requires SPA

- *Salmonella* - associated with bacteremia

- *Candida* - indwelling catheters, Ab Rx

- *S. aureus* - invades kidney from blood

- SCN - males w/ structural abnormality
RARE ORGANISMS

- *Corynebacterium urealyticum* – possesses strong urease – struvite stones; obstructive uropathy, renal transplant
- *Aerococcus* – similar to *Enterococcus*; elderly males w/ underlying urologic problems
- *Gardnerella vaginalis* & *Haemophilus influenzae* – rare pathogens
- *Candida* – healthcare associated; DM, neoplasms, catheterization, antibiotic/steroid use, neonates; often asymptomatic; no quantitative criteria
LABORATORY DIAGNOSIS

- Indication is key
- May not be indicated for non-pregnant otherwise healthy females with frequency, urgency, dysuria
- Indicated for infants, males, asymptomatic pregnant females, catheter or instrument associated HAI UTI, renal transplant, urologic disorders, diabetes, suspected pyelonephritis, prostatitis, epididymitis, relapse
LABORATORY DIAGNOSIS

- If indicated – perform
  - Results can aid management
- If not indicated – “don’t do it!”
  - Positive results - Ab Rx, CDI, resistance
- If uncertain - “UA with culture if indicated”
  - Use stringent criteria – WBC >10/hpf
  - Other criteria – low specificity
SPECIMENS

- First morning specimen
- SPA – gold standard/safe; infants, some adults, pregnant females; anaerobic culture
- Straight catheter – discard 1st few mLs, aseptic technique; 1-5% risk of infection
- Pediatric bag – negative culture rules out UTI; positive are often due to contamination
SPECIMENS

- Foley catheter
  - Use collection port
  - Clamp tubing
  - Do not culture catheter or bagged urine
  - **MUST** change Foley if >72 hrs
  - CAUTI
SPECIMENS

Straight catheter

Foley catheter

Suprapubic aspirate

Pediatric bag
CCMS urine; collection technique critical

Cleanse with towelettes as follows:

- Males – hold foreskin back; clean urogenital meatus;
- Females - separate the labia; clean urogenital meatus; keep the labia separated while collecting urine

- Urinate a small amount into toilet
- Place cup under urine stream; when full, finish urinating into toilet; recap cup
SPECIMENS

- Transport/Storage
  - Urine is excellent growth medium
  - Culture ASAP
  - If delayed > 2 hours
    - 4°C up to 24 hours
    - Borate preservative - works well (24-48 hrs), toxic to bacteria if ≤ 3 mL collected
SPECIMEN COLLECTION

Sterile cups

Borate Preservative System
SCREENING METHODS

- Microscopic/dipstick UA
- Gram stain
- Bioluminescence - bacterial ATP - light
- Filtration/Staining - Bac-T-Screen
- Growth dependent/flow cytometry
- All the above perform better @ ≥10^5 CFU/mL
URINALYSIS

- Non-specific – cloudiness, blood tinged
- Pyuria – leukocyte esterase or >5-10 WBC/hpf of unspun urine; sensitivity/specificity (>5) - 80-85%
  - Reflex - “UA with culture if indicated”; WBC >10/hpf
- Nitrituria – nitrate reducing bacteria; sensitivity – 39-69%; specificity 90-93%
- Leukocyte esterase + nitrites (either); 86%/67%
- Hematuria/proteinuria/bacteriuria - not sensitive or specific
- White cell casts - pyelonephritis
URINALYSIS

Dipstick UA

WBCs

Bacteria
Must have signs/symptoms of UTI e.g. frequency, urgency, dysuria, fever, etc., or other well established indication

Normal flora - urine sterile; urine specimens may not be contaminated w/ urethral/rectal/vaginal flora (6-38%) including potential pathogens

If culture performed w/o indication
- Growth a good possibility
- Unnecessary treatment – CDI, resistance
- CAUTI increased
CULTURE

- Symptomatic - 1 spec; asymptomatic* – 2
- Noninvasive (CCMS, foley, pedi bag) - 1 µL
- Invasive specimens (SPA, SC) – 10 µL
- Media - monomicrobial & gram negative bacteriuria the rule - BAP + MAC (EMB) ± PEA (CNA); chromogenic media
- Incubation - 35°C; 18-48 hours
CULTURE

- Quantitative culture - separate true UTI from contamination
- Classically - $\geq 10^5$ CFU/mL - UTI; $< 10^5$ CFU/mL contamination
- Reculture as test-of-cure – not recommended except for pregnant women, high risk patients
## GUIDELINES - NONINVASIVE

<table>
<thead>
<tr>
<th># Isolates</th>
<th>CFU/mL</th>
<th>Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; 10,000</td>
<td>MMI (minimal morphologic identification)</td>
</tr>
<tr>
<td></td>
<td>≥ 10,000</td>
<td>ID/AST (identification/antimicrobial susceptibility testing)</td>
</tr>
<tr>
<td>2</td>
<td>Both &lt; 10,000</td>
<td>MMI (both)</td>
</tr>
<tr>
<td></td>
<td>Both ≥ 10,000</td>
<td>ID/AST (both)</td>
</tr>
<tr>
<td></td>
<td>1 &lt; 10,000</td>
<td>MMI</td>
</tr>
<tr>
<td></td>
<td>1 ≥ 10,000</td>
<td>ID/AST</td>
</tr>
<tr>
<td>≥3</td>
<td>1 ≥ 100,000</td>
<td>ID/AST</td>
</tr>
<tr>
<td></td>
<td>2 &lt; 10,000</td>
<td>MMI</td>
</tr>
<tr>
<td></td>
<td>Any other</td>
<td>MMI; “mixed culture; recollect if indicated”</td>
</tr>
</tbody>
</table>

Noninvasive – CCMS, foley, pedi bag
Culture 1 µL; incubate 16-24 hrs
ID/AST – as appropriate
**GUIDELINES - INVASIVE**

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Invasive – straight cath, SPA, cystoscopy, nephrostomy
Culture 10 µL; incubate 48hrs
ID/AST – as appropriate
INOCULATION/CULTURE

1. Primary Inoculation
2. Streak at Right Angles
CHROMOGENIC MEDIA

- *E. coli*
- coliform
- Proteus
- enterococci
CULTURE PROBLEMS

- Specimen collection - females, infants
- Chronic catheterization - colonization; symptoms hard to assess; significance of 6-8 organisms?
- Culture+ without appropriate indications
MIXED CULTURE

- ≥ 3 bugs)
  - <5% if collected & transported appropriately
  - Up to 50% are not – usually contamination
CULTURE PROBLEMS

- Nursing home patients - poor positive predictive value
- Symptomatic patients w/ $<10^5$ CFU/mL
  - Females + classic symptoms + coliforms
    - $\geq 10^5$ CFU/mL (50% sens/99% spec)
    - $\geq 10^2$ CFU/mL (95% sens/85% spec)
- Pregnant females with GBS – marker of heavy vaginal/rectal colonization
FALSE NEGATIVE CULTURES

- Dilution - forcing fluids
- Antibiotic therapy - high urine concentration
- “Sterile pyuria” – WBC >5 w/ negative culture
  - Injury to UT, catheterization, vesicoureteral reflux, interstitial cystitis, polycystic kidney disease, tumor, staghorn calculi, stones, abnormal UT, contiguous infection
  - Anaerobes, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycobacterium tuberculosis*, *Leptospira*, systemic fungal infection
CULTURE ID & AST

- Core function of Microbiology Lab
- No growth - no problem
- Growth - identify isolate(s)
  - Necessary to determine etiology, clinical significance, potential therapy
  - Conventional methods
    - Microscopy/Colonial Morphology/Biochemical Reactivity
    - TAT – 24-72 hours after appearance of visible colonies
CONVENTIONAL ID

Microscopy

Colony Morphology

Biochemical Profile
MALDI-TOF

- Matrix-assisted laser desorption/ionization – Time of Flight
- Proteins & peptides arranged in a spectrum of increasing mass
- Pattern or “fingerprint” characteristic for individual organism
- bioMérieux – Vitek MS®; Bruker – Biotyper®
- TAT – 10 minutes
MALDI-TOF

![Image of MALDI-TOF instrument]

**Adjusted Normalized Peaklists**

<table>
<thead>
<tr>
<th>Spectrum</th>
<th>Analyte Name</th>
<th>Analyte ID</th>
<th>Organism (best match)</th>
<th>Score Value</th>
<th>Organism (second best match)</th>
<th>Score Value</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Escherichia coli DH5alpha REL</td>
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<td>Escherichia coli DH5alpha REL</td>
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<td>Escherichia coli ATCC 25922 THL</td>
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<td>2</td>
<td>Burkholderia multivorans LMG 14293 HAM</td>
<td>MB 20</td>
<td>Burkholderia multivorans LMG 14293 HAM</td>
<td>2.457</td>
<td>Burkholderia dolosa DSM 16088 HAM</td>
<td>1.855</td>
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<td>3</td>
<td>Burkholderia multivorans LMG 14293 HAM</td>
<td>MB 20</td>
<td>Burkholderia multivorans LMG 14293 HAM</td>
<td>2.462</td>
<td>Burkholderia dolosa DSM 16088 HAM</td>
<td>1.996</td>
</tr>
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AST - Reminders

When performed
- Isolate clinically significant (pathogen)
- Susceptibility pattern unpredictable
- Standardized method available

Utility
- AST results may not predict clinical efficacy
- Purpose of AST is to detect phenotypic RESISTANCE - high correlation with clinical failure
AST - TAT

- Conventional AST – 18-24 hours
- Vitek XL AST (bioMérieux) – 6-12 hrs
- MAST (Greiner Bio-One) – 2-4 hrs
- Accelerate (Pheno) – 7 hrs
- Faster time to definitive/directed antibiotic therapy
WORKFLOW

- Faster TAT – nice, but…
- Need to maximize speed advantages
  - Initial read of cultures – 18 hrs
  - If no growth – final
  - If growth – MALDI ID & rapid AST
    - Results for ID in 1 hr
    - Results for AST 6-12 hrs later
- That the “pitch”, but need a “catcher” (ASP)
What’s The Bottom Line?

- Organism identifications on day 1 (18-24 hours after specimen processing) instead of day 2
- Reported AST results (later) on day 1 (4-12 hours after identification) instead of day 2
- Clinical utility of faster results depends on what you do with the information & how fast you do it
- Antibiotic stewardship intervention vital for optimal utilization of faster results
IMPACT

- Shorter time to identification & AST
  - ASP key to getting
    - Shorter time to effective therapy
    - Shorter time to optimal therapy
    - Reduction in length of antimicrobial therapy
    - Reduced LOS
    - Reduction in ICU LOS


SUMMARY

- Key features of laboratory diagnosis of UTI
  - Perform only when indicated
  - Appropriate specimen collection/transport vital
    - “Garbage in → garbage out”
  - Awareness of limitations
  - Rapid ID & AST with robust ASP
    - Significant clinical impact
LABORATORY DIAGNOSTIC ASPECTS OF UTI – POTENTIAL IMPACT ON ASP

Questions?
Comments?
What is the MAJOR purpose behind the strategy of using the presence of pyuria (≥10 WBC/hpf) as the sole criterion for performing a urine culture when “UA with culture if indicated” is ordered?

a. To culture urine only when there is a high likelihood of UTI (specificity)

b. To ensure that no UTIs are missed (sensitivity)

c. To reduce urine cultures for the overworked Microbiology lab

d. To ensure that the lab works up all microorganisms that grow from culture

e. To annoy physicians
Assessment Question

What is the MAJOR purpose behind the strategy of “selective reporting” of antimicrobial susceptibility testing (AST) results?

a. Control pharmacy costs
b. Drive usage toward oral therapy
c. Reduce usage of fluoroquinolones
d. Force physicians to call the lab for AST results
e. Preserve the utility of currently available broad spectrum antibiotics
Assessment Question

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