Reducing Prostate Biopsy Related Infections: What is the Role of the Microbiology Lab?

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April 5, 2016
Disclosures

I have no financial disclosures relevant to the content of this presentation
Objectives

- Describe the emerging problem of prostate biopsy associated infections.
- Evaluate screening vs. alternative prophylaxis as an approach to minimizing infections.
- Discuss how a screening plan for resistant organisms might be implemented.
Outline

• Prostate Cancer Screening

• Complications of Biopsy

• Fluoroquinolone Resistance and Colonization

• Risk Factors for Infection

• Approaches to Infection Prevention

• The Role of the Laboratory in Screening
Prostate Cancer Screening

- 1 in 7 chance of developing prostate cancer
- 1 in 30 chance of dying from the disease
- 1992: ACS recommends PSA for men >50
What is the PSA?

- Prostate Specific Antigen
  - Secreted by prostate epithelial cells
  - Detectable in blood
  - Non-specific elevations
    - Prostatitis
    - UTI
    - Benign Prostatic Hyperplasia
    - Ejaculation
    - Digital Rectal Exam
    - Medications and Herbal Supplements
What is a Normal PSA?

• Historic threshold 4.0 ng/mL

• No level allows “rule out”

• Recent trials have used 2.5-4.0 ng/mL as cutoff

• Positive correlation between ↑ levels and Pca

• Prostate Cancer Prevention Trial
  • Over 7 year study 15.2% had cancer with PSA <4.0
    • Pca prevalence 6.6% with PSA <0.5 ng/mL
    • Pca prevalence 26.9% with PSA 3.1-4.0 ng/mL
  • N Engl J Med 350:2239-2246
What if the Result is Abnormal?

• NCCN Guidelines recommend action >3.0 ng/mL
  • Evaluation for benign disease
  • Repeat PSA
  • DRE
  • Use this data to inform biopsy decision
Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, PhD, on behalf of the U.S. Preventive Services Task Force*
### Table 3. PSA-Based Screening for Prostate Cancer*

#### Harms of screening

At least 1 false-positive screening PSA test result

**Most positive test results lead to biopsy.**

100–120 in 1000

Of men having biopsy, up to 33% will have moderate or major bothersome symptoms, including pain, fever, bleeding, infection, and temporary urinary difficulties; 1% will be hospitalized.

#### Prostate cancer diagnosis

Although a diagnosis of prostate cancer may not be considered a harm, currently 90% of diagnosed men are treated and, thus, are at risk for the harms of treatment. A large majority of the men who are being treated would do well without treatment. A substantial percentage of these men would have remained asymptomatic for life.

#### Complications of treatment (among persons who are screened)†

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Develop serious cardiovascular events due to treatment</td>
<td>2 in 1000</td>
</tr>
<tr>
<td>Develop deep venous thrombosis or pulmonary embolus due to treatment</td>
<td>1 in 1000</td>
</tr>
<tr>
<td>Develop erectile dysfunction due to treatment</td>
<td>29 in 1000</td>
</tr>
<tr>
<td>Develop urinary incontinence due to treatment</td>
<td>18 in 1000</td>
</tr>
<tr>
<td>Die due to treatment</td>
<td>&lt;1 in 1000</td>
</tr>
</tbody>
</table>

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*PSA = prostate-specific antigen.

† The table is adapted from Wilt and Schwartz (2010). Calculations of the benefits and harms rely on assumptions and are, by nature, somewhat imprecise. Estimates should be considered in the full context of clinical decision making and used as stimulants, not decision makers.

‡ The best evidence of possible benefit of PSA screening is in men aged 55–69 y.

§ The best evidence of possible benefit of PSA screening is in men aged 55–69 y. A recent study of the harms associated with PSA testing found that the benefits may outweigh the harms.

The table reflects a distribution of 66% surgical treatment, 34% radiation, and 10% observation (see Appendix 2, available at www.aann.org, for more details about assumptions and references). Other harms of radiation, such as bowel damage, are not shown.
Who Should be Screened?

• AUA Guideline:
  • Men <40 should not have routine PSA screening
  • Men 40-54 should not have routine screening, evaluate risks
  • Men 55-69 shared decision making process
  • Men ≥70 should not have routine PSA screening

• US Preventative Task Force Recommendation:
  • 2008: Men ≥75 not have routine screening
  • 2012: Screening risks outweigh benefits in men of all ages
“Approximately ten years after my discovery, Beckman Coulter (formerly Hybritech) developed the first validated blood test for PSA levels. At first, it was only used as I had envisioned – for monitoring of patients after treatment for PrCa, and it was approved by the FDA for this purpose in 1986. But more and more people started using the test off label to screen for PrCa. It was like a tsunami. In 1994, the FDA approved the test in concert with a digital rectal examination (DRE) for screening, i.e., the diagnosis of PrCa in asymptomatic men. On the basis of the submitted data, I believe the FDA made a terrible mistake – one that has resulted in the overdiagnosis and overtreatment of millions of men with their attendant morbidities.”
Anatomy of the male genitourinary tract in relation to transrectal ultrasound (TRUS)–guided prostate biopsy
Common Complications

• Bleeding
  • 1% have severe bleeding requiring hospitalization
  • Hematuria, hematospermia, and rectal bleeding

• Pain
  • 90% report discomfort, many would not repeat without anesthesia

• Infection
  • GU tract → sepsis
Infectious Complications

- 4% febrile UTI
- Up to 0.6% severe sepsis or septic shock
- Rarely endocarditis, osteomyelitis, epidural abscess

- 30 day hospitalizations due to infections only ↑ between 1991 and 2007
  - J Urol 186:1830-1834

- 30 day UTI or bacteremia incidence ↑ 0.71/100 to 2.15/100 biopsies between 2002 and 2011
  - Eur Urol 62:453-459
What is causing these infections?

- 75-90% *E. coli*
- Majority fluoroquinolone resistant
- Many resistant to additional antimicrobial agents
  - ESBL/cephalosporin resistance
  - Gentamicin resistance
    - Clin Infect Dis **57**:267-274
- Patient’s own colonizing bacteria most common source
  - Clin Infect Dis **60**:979-987
- AUA Best Practice Policy Statement recommends fluoroquinolone or cephalosporin as pre-biopsy prophylaxis
What Causes Fluoroquinolone Resistance?

- Fluoroquinolone target is type II topoisomerase enzymes: DNA gyrase and Topoisomerase IV

- Bacterial DNA is supercoiled to condense and pack into cell by topoisomerases

- Topoisomerases necessary to relieve supercoiling for DNA replication and to separate chromosomes after replication

- Drug binding to enzyme/DNA complex causes breaks

Mechanisms in Medicine Video
https://www.youtube.com/watch?v=IkKZ_gxAOXI
Bacterial type II topoisomerases

Negatively supercoiled
Gyrase
Topo IV

Relaxed
Gyrase
Topo IV

Positively supercoiled

Interlinked chromosomes


Liam S. Redgrave, Sam B. Sutton, Mark A. Webber, Laura J.V. Piddock

Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success

What Causes Fluoroquinolone Resistance?

- Most resistance mediated by mutations in target site

- Less common:
  - Plasmid Mediated Quinolone Resistance (PMQR)
  - Porin Mutation
  - Efflux
Fluoroquinolone Resistance

- Historically good activity vs Enterobacteriaceae

- >77,000 clinical isolates tested in 2000, ~95% cipro susceptible

- Resistance rates increased over following decade

- 2009-2011 US UTI isolates
  - CA infections: 28.5% non-ESBL E. coli cipro resistant
  - HA infections: 36.3 % non-ESBL E. coli cipro resistant
    - Clin Ther 35:872-877
Fluoroquinolone Resistance

- Colonization with fluoroquinolone resistant bacteria in men undergoing prostate biopsy: 22.8%
  - BJU Int doi:10.1111/bju.13402

- Prior to prophylaxis: 12.8%

- After prophylaxis: 20.4%
  - Int J Antimicrob Agents 43:301-309
Fluoroquinolone Resistance

• Study of mothers and twins found 20% had cipro resistant *E. coli* in stool over 2.5 year period

• No relationship between cipro exposure and resistance

• 51% of isolates resistant to at least one additional drug
  • *J Infect Dis* 212:1862-1868.
Post-biopsy Infection Risk Factors

- Colonization with fluoroquinolone resistant *E. coli*
  - 6.6% vs 1.1% developed infection
  - 4.4% vs 0.9% required hospitalization within 30 days for infection
    - *J Urol* 192:1673-1678

- Exposure to antibiotics within 6 months

- Hospital employees and their families

- People with international travel
Infection Prevention Approaches

- Pre-biopsy enema
- Povidone-iodine or chlorhexidine disinfection of rectum
- Bisacodyl supposotories
- Disinfection of biopsy needle with 10% formalin between cores
- Transperineal approach
Infection Prevention Approaches

1. Augmented prophylaxis
   • Addition of antimicrobial
     • Gentamicin
     • Cefazolin
     • Piperacillin/tazobactam

2. Targeted Prophylaxis
   • Single agent which has been demonstrated susceptible
A Statewide Intervention to Reduce Hospitalizations after Prostate Biopsy

Paul R. Womble, Susan M. Linsell, Yuqing Gao, Zaojun Ye, James E. Montie,* Tejal N. Gandhi, Brian R. Lane, Frank N. Burks and David C. Miller†,‡ for the Michigan Urological Surgery Improvement Collaborative

From the Department of Urology (PRW, SML, YG, ZY, JEM, DCM) and Division of Infectious Disease (TNG), University of Michigan, Ann Arbor, Department of Urology, Spectrum Health Medical Group, Grand Rapids (BRL), and Department of Urology, Oakland University William Beaumont School of Medicine, Royal Oak (FNB), Michigan

Population:
30 Michigan urology practices

Study Design:
Retrospective data collection using conventional prophylaxis (n=5,028)
Prospective data collection using either augmented or targeted (n=4,087)

Outcome:
Infection related hospitalization within 30 days
Details and Limitations

Culture conditions:
Stool or rectal swabs
MacConkey with 10 µg/mL ciprofloxacin
ID and sus any growth

Table 2. Patterns of prophylactic antibiotic use before and after implementation of QI initiative

<table>
<thead>
<tr>
<th></th>
<th>No. Pre-Implementation (%)</th>
<th>No. Post-Implementation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totals</td>
<td>5,028 (100)</td>
<td>4,087 (100)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>3,458 (68.8)</td>
<td>238 (5.8)</td>
</tr>
<tr>
<td>Combination/augmented</td>
<td>1,184 (23.5)</td>
<td>3,625 (88.7)</td>
</tr>
<tr>
<td>Culture directed</td>
<td>0 (0)</td>
<td>215 (5.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>386 (7.7)</td>
<td>9 (0.2)</td>
</tr>
</tbody>
</table>
A Statewide Intervention to Reduce Hospitalizations after Prostate Biopsy

**Figure 1.** Unadjusted (A) and risk adjusted (B) rate of infection related hospitalizations before and after implementation of QI intervention (adjusted for age, history of prior biopsy, prostate size and PSA). Patients were excluded from model if covariate values were missing.
A Statewide Intervention to Reduce Hospitalizations after Prostate Biopsy

Figure 2. Unadjusted infection related hospitalizations after prostate biopsy by MUSIC pathway.
Findings:
• >90% of infections were caused by *E. coli* (pre and post)
  • 78.2% cipro resistant pre-intervention
  • 63.2% cipro resistant post-intervention
  • 8.3% received culture directed intervention
Conclusions:

• Statewide intervention reduced prostate biopsy related infections by 53%

• There was no significant difference between targeted and augmented prophylaxis interventions
Population:
13 Kaiser Permanente urology departments in California

Study Design:
Retrospective data collection using empirical prophylaxis (n=3,553)
  • Empirical defined as monotherapy or augmented therapy
Retrospective data collection using targeted (n=1,802)

Outcome:
Sepsis within 30 days
Details and Limitations

Culture conditions:
Stool or rectal swabs
MacConkey with 10 µg/mL ciprofloxacin
ID and sus any growth
Findings:

• Prevalence of cipro resistant *E. coli* on screen: 25%
• Incidence of sepsis in targeted group: 0.44%
• Incidence of sepsis in empirical group: 0.56%
Findings:

- Targeted Group, 8 infections
  - 5 of 8 with cipro sensitive organisms after cipro prophylaxis
    - 3 E. coli, 1 Klebsiella pneumoniae, 1 Pseudomonas aeruginosa
  - 2 of 8 with cipro R E. coli on screen given gentamicin (tested sus), septic with cipro R, gent R E. coli
  - 1 of 8 with cipro R E. coli on screen given TMP/SMX (tested sus), septic with cipro S, TMP/SMX R Proteus mirabilis
Findings:

- Empirical Group, 20 infections
  - 19 of 20 infections caused by *E. coli*, 1 by *P. mirabilis*
  - 15 of 19 were cipro resistant *E. coli* given cipro ± gent
  - 4 of 19 were cipro sus *E. coli* given cipro ± gent
Conclusions:

• Overall reduction in infections was not statistically different
  • 87.5% who developed sepsis received correct antibiotic with targeted prophylaxis
  • 20% who developed sepsis received correct antibiotic with empirical prophylaxis

• Targeted prophylaxis allows physicians to limit use of multiple antimicrobials
### 2015 Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Size</th>
<th>Design*</th>
<th>Significant Reduction</th>
<th>Culture protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summers et al., 2015</td>
<td>2759/166</td>
<td>empirical vs targeted</td>
<td>No</td>
<td>10 µg cipro MAC</td>
</tr>
<tr>
<td>Liss et al., 2015</td>
<td>3553/1802</td>
<td>empirical vs targeted**</td>
<td>No</td>
<td>10 µg cipro MAC</td>
</tr>
<tr>
<td>Dai et al., 2015</td>
<td>173/314</td>
<td>empirical vs targeted</td>
<td>No</td>
<td>1 µg cipro MAC</td>
</tr>
<tr>
<td>Cook et al., 2015</td>
<td>264/242</td>
<td>empirical vs targeted</td>
<td>Yes</td>
<td>1 µg cipro MAC</td>
</tr>
<tr>
<td>Womble et al., 2015</td>
<td>5028/4087</td>
<td>empirical vs targeted or augmented</td>
<td>Yes***</td>
<td>10 µg cipro MAC</td>
</tr>
<tr>
<td>Farrell et al., 2015</td>
<td>543/143</td>
<td>empirical vs targeted</td>
<td>Yes</td>
<td>10 µg cipro MAC</td>
</tr>
</tbody>
</table>

* Emperical prophylaxis encompasses non-culture directed prophylaxis chosen by physician, typically single agent and most commonly ciprofloxacin.

* *This study combines single agent (75%) and augmented (25%) prophylaxis into a single category of emperical prophylaxis.
Study Conclusions

• Several small studies have shown a trend toward reduction in infections with targeted prophylaxis, but not powered adequately to detect differences

• Difficult to compare studies as lab procedures and study design differs substantially
  • Definitions used in studies vary (standard, empirical, targeted, augmented, etc.)
  • 1 µg/mL vs 10 µg/mL media
  • Culture collection: 30 days to shortly before biopsy
  • Susceptibility testing protocols differ
  • Response to positive screening culture differs

• 2015 meta-analysis indicated targeted prophylaxis in 27 patients would prevent one additional infection
How do I Implement Screening? There is no Standardized Protocol

- Cipro MacConkey: 1 µg/mL and 10 µg/mL commercially available
- CLSI Breakpoint for Enterobacteriaceae vs cipro:
  - S ≤1 µg/mL, I = 2µg/mL, R ≥ 4µg/mL
- What about organisms with MIC of 2-10µg/mL?
Ciprofloxacin / Escherichia coli
International MIC Distribution - Reference Database 2016-04-04

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

M IC
Epidemiological cut-off (ECOFF): \( \leq 0.064 \) mg/L
Wildtype (WT) organisms: \( \leq 0.064 \) mg/L


http://mic.eucast.org/

16702 observations (55 data sources)
How do I Implement Screening?
There is no Standardized Protocol

- Cipro MacConkey: 1 µg/mL and 10 µg/mL commercially available
- CLSI Breakpoint for Enterobacteriaceae vs cipro:
  - S \leq 1 µg/mL, I = 2µg/mL, R \geq 4µg/mL
- What about organisms with MIC of 2-10µg/mL?

- EUCAST data <3% of E. coli with MIC 2-8µg/mL
- Cipro resistant isolates from men undergoing prostate biopsy had MIC>32µg/mL
- Comparison of direct plating vs broth enrichment using 1 µg/mL and 10 µg/mL media found no significant difference in detection
Pros and Cons

- **Pros:**
  - Allow selection of most narrow spectrum antimicrobial
  - Possibly reduce infectious complications

- **Cons:**
  - Possible additional visit for screening culture
  - No standardized procedures
  - Possibly doesn’t reduce infectious complications

- **To Be Determined**
  - Optimal screening window
  - Best culture approach
  - Reporting algorithms
Conclusions

• Large scale, standardized studies are needed to determine efficacy of screening vs augmented prophylaxis

• For those who choose to implement, should work closely with clinical colleagues (urology, ID, pharmacy) to determine best use
Thank you!