Urinary Tract Infections

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Epidemiology of UTIs in the United States

- 8 million physician visits/year
- 10.8% annual prevalence
- 40%–50% lifetime prevalence in women
- 1 in 3 women will require antimicrobial therapy before 24 years of age
- 0.5–0.7 episodes/person-year in sexually active women
- $1 billion/year for evaluation and treatment

Pathogenesis

- Rectal and/or vaginal reservoirs
- Colonization of perianal area
- Bacterial migration to perivaginal area
- Bacteria ascend through urethra to bladder
- Intercourse may contribute urethral colonization and ascending infection
- ASB in 1st trimester of pregnancy may cause pyelonephritis in 3rd trimester

Foxman B. Am J Med. 2002;113(Suppl):5S-13S.
Urinary Tract Infection

Upper
- Pyelonephritis (± bacteremia)

Lower
- Cystitis (approx. 30% occult pyelonephritis)
- Asymptomatic bacteriuria (ASB)
- Urethral syndrome

Clinical Characteristics

<table>
<thead>
<tr>
<th>Uncomplicated UTI</th>
<th>Complicated UTI</th>
<th>Uncomplicated Pyelonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consequences</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Differential Diagnosis of Bacteriuria

Patient Symptomatic?  
- no: Asymptomatic bacteriuria
  - yes: Complicating Factors?
    - no: Recurrent Episode?
      - no: Uncomplicated cystitis, urethritis, or vaginitis
      - yes: Pyelonephritis
    - yes: Complicated UTI


Signs and Symptoms of UTI

Subjective symptoms
- Frequency
- Dysuria
- Urgency / Hesitancy
- Subrapubic or low back pain

Objective signs (not required for uncomplicated UTI)
- Bacteriuria  
  \(10^2 \text{ to } \geq 10^5\) colony-forming units/mL
- Pyuria (WBC >10/mm³)

Laboratory Diagnosis of UTI

Urinalysis
- 10 WBC/hpf is the usual upper limit of normal
- Positive result on leukocyte esterase dipstick test correlates well for detecting >10 WBC/hpf, with a specificity of 65%–95%, and sensitivity of 75%–95%
- Positive nitrate dipstick test result for bacteriuria is only moderately reliable; false-negative results are common
- Urine cultures not necessary in women with uncomplicated UTI

Risk Factors and Pathogenesis

Risk Factors
- Sexual activity with different partners
- Diaphragm or spermicide use
- History of prior UTI

Pathogenesis
- Uncomplicated UTI: mostly ascending uropathogens
  - \(E.\ coli, S.\ saprophyticus,\ Proteus\ spp.,\ Klebsiella\ spp.\)

Antibiotic Selection Considerations

- Local antibiotic resistance patterns
- Pharmacokinetics
  - Drug concentration in urinary tract (renal excretion of active drug)
  - Once-daily vs multiple daily doses
- Effects on normal enteric and vaginal flora
- Safety (adverse events, allergies)
- Patient age
- Prior antibiotic courses


Treatment of Uncomplicated UTI

Antibiotic Therapy

- 3-day course recommended
  - TMP/SMX
  - Fluoroquinolone
- Single-dose therapy is less effective
  - Especially with β-lactams
- 7-day regimens are no more effective than 3 days
  - Increased cost and side effects


Etiology of Uncomplicated UTIs in the US (Women 15–50 years old)

Gram-Negatives
- Escherichia coli (72%)
- Klebsiella species (6%)
- Proteus species (4%)
- Other (5%)

Gram-Positives
- Enterococcus species (5%)
- Other Gram-positive organisms (7%)

Treatment Options for Uncomplicated UTI

TMP/SMX resistance <20%
- TMP/SMX — 3 days
- TMP — 3 days

TMP/SMX resistance >10%–20%
- Fluoroquinolone — 3 days
- Nitrofurantoin — 7 days

Nicolle LE. Am J Med. 2002;113:35S-44S.

Gram-Negative Surveillance:
TRUST 6 (2002), % Susceptible

<table>
<thead>
<tr>
<th>Urine Isolates</th>
<th>n</th>
<th>LEVO</th>
<th>CIPRO</th>
<th>AMP</th>
<th>TMP/SMX</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>871</td>
<td>93.7</td>
<td>93.6</td>
<td>60.8</td>
<td>80.6</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>462</td>
<td>96.1</td>
<td>93.9</td>
<td>3.7</td>
<td>92.9</td>
</tr>
<tr>
<td>E. cloacae</td>
<td>179</td>
<td>93.3</td>
<td>87.2</td>
<td>12.8</td>
<td>82.7</td>
</tr>
<tr>
<td>C. freundii</td>
<td>98</td>
<td>89.8</td>
<td>84.7</td>
<td>40.8</td>
<td>72.4</td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>374</td>
<td>88.0</td>
<td>82.6</td>
<td>85.6</td>
<td>81.3</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>290</td>
<td>64.1</td>
<td>64.5</td>
<td>NA</td>
<td>2.1</td>
</tr>
</tbody>
</table>

N=Not Available. 36 geographically distributed sites.
In vitro data does not necessarily correlate with clinical results. In clinical trials, levofloxacin has demonstrated comparable efficacy to ciprofloxacin. No comparative clinical data are available for ampicillin and TMP/SMX.


Susceptibility of UTI Isolates From Women (15–50 Years of Age)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>AMP</th>
<th>CIPRO</th>
<th>LEVO</th>
<th>NFTN</th>
<th>TMP/SMX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacter spp.</td>
<td>3</td>
<td>96</td>
<td>98</td>
<td>51</td>
<td>95</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>98</td>
<td>67</td>
<td>83</td>
<td>98</td>
<td>NT</td>
</tr>
<tr>
<td>E. coli</td>
<td>98</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>82</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>1</td>
<td>99</td>
<td>98</td>
<td>97</td>
<td>92</td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>92</td>
<td>98</td>
<td>98</td>
<td>1</td>
<td>94</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>NA</td>
<td>74</td>
<td>72</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>S. saprophyticus</td>
<td>29</td>
<td>99</td>
<td>100</td>
<td>99</td>
<td>93</td>
</tr>
<tr>
<td>S. aureus</td>
<td>16</td>
<td>95</td>
<td>95</td>
<td>99</td>
<td>97</td>
</tr>
</tbody>
</table>

N=Not Available. In vitro data does not necessarily correlate with clinical results. In clinical trials, levofloxacin has demonstrated comparable efficacy to ciprofloxacin. No comparative clinical data are available for ampicillin, TMP/SMX, or nitrofurantoin.

Recurrent Uncomplicated UTI: Pathogenesis and Epidemiology

Pathogenesis
- Most cases of recurrent UTI due to reinfection, usually E. coli (not always from the same strain as the original infection)

Epidemiology
- 20%–30% of young women with uncomplicated cystitis have recurrent UTI
- Risk factors: sexual intercourse, spermicide, first UTI at early age, maternal history of UTI

Management of Recurrent UTI

Three treatment options:
- Long-term, low-dose prophylaxis (usually 6–12 months)
  - TMP/SMX, TMP, nitrofurantoin, norfloxacin
- Postintercourse, low-dose prophylaxis
  - Single dose of TMP/SMX, TMP, nitrofurantoin, cephalexin, fluoroquinolone
- Self-treatment and diagnosis (3 days)
  - TMP/SMX, TMP, fluoroquinolone

Complicated Urinary Tract Infections

- Complicated UTI is a urinary tract infection in a patient with a functionally, metabolically, or anatomically abnormal urinary tract, including:
  - Foreign body (catheter, stent)
  - Obstruction (calculi, congenital anomaly, prostatic disease, stricture, tumor)
Catheter

- Foley catheter developed at SPRMC (Regions)
- Foreign body
- Insertion can be traumatic leading to infection
- Provides mechanism for bacteria to ascend into bladder
- Usual symptoms of UTI hidden by presence of catheter (ASB vs UTI)
- Antibiotic delivered to bladder is immediately drained away

Risk Factors for Complicated Urinary Tract Infection

- Advanced age, debility
- Male gender
- Hospitalization
- Long-term care
- Diabetes mellitus
- Functional/anatomic abnormalities
- Immunosuppression or suppressive drugs
- Pregnancy or menopause
- Catheter or stent
- Stones in bladder or urinary tract
- Recent antibiotic use
- Recent urinary tract instrumentation
- Renal transplant
- Symptoms >7 days

Clinical Implications of Complicated UTI

- Pathogens: wide range of Gram-negative and Gram-positive organisms
- Resistance to TMP/SMX common
- Therapy: 7–14 days of antimicrobial therapy
- Follow up: repeat urinalysis and culture
  - 1–2 weeks after completion of antibiotic therapy

Complicated UTI Etiology

<table>
<thead>
<tr>
<th>Bacterial Uropathogen</th>
<th>Prevalence in Complicated UTI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>21 – 54</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>1.9 – 17</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>1.9 – 9.6</td>
</tr>
<tr>
<td>Citrobacter species</td>
<td>4.7 – 6.1</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>0.9 – 9.6</td>
</tr>
<tr>
<td>Providencia species</td>
<td>18</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>2 – 19</td>
</tr>
<tr>
<td>Enterococci species</td>
<td>6.1 – 23</td>
</tr>
</tbody>
</table>


Resistance in UTIs in the Elderly

<table>
<thead>
<tr>
<th>Organism</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMP^1</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>57</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>0</td>
</tr>
<tr>
<td><em>Proteus spp.</em></td>
<td>98</td>
</tr>
<tr>
<td><em>P. stuartii</em></td>
<td>60</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>–</td>
</tr>
</tbody>
</table>


Acute Pyelonephritis: Epidemiology and Pathogenesis

**Epidemiology**
- About 250,000 patients per year in the US

**Pathogenesis**
- Infection of the upper urinary tract
- Implicated pathogens include:
  - *E. coli*
  - *P. mirabilis*
  - *K. pneumoniae*

Symptoms of Pyelonephritis

Symptoms develop rapidly (<24 hours) and may include:
- Fever >38°C
- Chills
- Nausea/vomiting
- Diarrhea
- Symptoms of cystitis
- Generalized muscle tenderness
- Flank pain


Treatment of Pyelonephritis

Eradicate pathogens in kidney and urothelium, and treat/prevent bacteremia
- Hospitalized patients: IV antibiotic first 48–72 hours, followed by 7 days of oral antibiotic therapy
  - Fluoroquinolone IV, then PO
  - Aminoglycoside ± ampicillin IV, then TMP/SMX PO or amox/clav
  - Third-generation cephalosporin IV, then TMP/SMX PO or amox/clav
- Ambulatory patients: 7–14 days of PO therapy with one of the antimicrobials above


IDSA Treatment Guidelines:
Acute Uncomplicated Pyelonephritis

Mild or moderate symptoms:
- Outpatient treatment (total of 7–14 days)

Oral treatment:
- Fluoroquinolone
- TMP/SMX, if uropathogen is known to be susceptible
- If Gram-positive pathogen: amoxicillin or amoxicillin-clavulanate

Antimicrobial In Vitro Resistance in Pyelonephritis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>72</td>
<td>57</td>
<td>NA</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>100</td>
<td>70</td>
<td>82</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>NA</td>
<td>98</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>


Bacterial Prostatitis Issues

Antibiotic Penetration
- Does the drug successfully get to the site of infection?

Pathogen Coverage
- Will the drug cover Gram-negative as well as Gram-positive pathogens?

Pill Burden
- Are there advantages for once-daily dosing?

Epidemiology and Pathogenesis

- 2 million US office visits annually for prostatitis
- Bacterial prostatitis (acute and chronic) accounts for 5%–10% of cases
- *E. coli* historically believed to be the predominant pathogen
- PCPs/urologists typically start patients on anti-infective therapy empirically

Distinguishing Features of Prostate Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Confirmed UTI</th>
<th>Prostate Exam</th>
<th>Prostatic Fluid WBC Culture</th>
<th>Response to Abx</th>
<th>Impaired Urinary Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP</td>
<td>Yes</td>
<td>Tender, warm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CBP</td>
<td>Usually</td>
<td>Varied</td>
<td>Yes</td>
<td>Slow</td>
<td>+/-</td>
</tr>
<tr>
<td>NBP</td>
<td>No</td>
<td>Varied</td>
<td>Yes</td>
<td>No</td>
<td>Poor</td>
</tr>
<tr>
<td>PD</td>
<td>No</td>
<td>Usually normal</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

ABP=acute bacterial prostatitis; CBP=chronic bacterial prostatitis; NBP=nonbacterial prostatitis; PD=prostatodynia.


Treatment

<table>
<thead>
<tr>
<th>Etiology</th>
<th>First-Line</th>
<th>Other Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bacterial prostatitis</td>
<td>Fluoroquinolone</td>
<td>TMP/SMX Amikacin Aminoglycoside + cephalosporin</td>
</tr>
<tr>
<td>Chronic bacterial prostatitis</td>
<td>Fluoroquinolone</td>
<td>TMP/SMX Tetracycline</td>
</tr>
<tr>
<td>Chronic pelvic pain syndrome</td>
<td>Fluoroquinolone</td>
<td>TMP/SMX Tetracycline</td>
</tr>
</tbody>
</table>


Clinical Symptoms Characterizing Chronic Prostatitis

- Frequent need to urinate
- Difficulty urinating (eg, weak stream and straining)
- Pain on urination, or that increases with urination
- Fatigue
- Pain (other than with urination) in the pelvic area
- Abdominal pain
- Arthralgia
- Myalgia
- Pain at other location

Evaluation of Patients With Chronic Prostatitis/CPPS

Mandatory
- History
- Physical examination, including DRE
- Urinalysis and urine culture

Recommended
- Lower urinary tract localization test
- Symptom inventory or index (NIH-CPSI)
- Flow rate
- Residual urine determination
- Urine cytology

DRE = digital rectal exam.
NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index.

Evaluation of Patients With Chronic Prostatitis

Optional
- Semen analysis and culture
- Urethral swab for culture
- Pressure-flow studies
- Video-urodynamics (including flow-EMG)
- Cystoscopy
- Transrectal ultrasound
- Pelvic imaging (US, CT scan, MRI)
- Prostate-specific antigen*

*Recommended for men >50 years or >40 years if African-American or men with a strong positive family history of prostate cancer.
EMG = electromyography; US = ultrasound; CT = computed tomography.
MRI = magnetic resonance imaging.

Recommended Treatment for Chronic Bacterial Prostatitis

Recommended:
- Fluoroquinolone for 28 days

Alternatives:
- Trimethoprim 28 days
- Doxycycline 28 days

Principles for Antibiotic Therapy

- Penetration in the prostate and prostatic fluid
  - Lipid soluble
  - Minimal binding to serum protein
  - Degree of ionization
- Activity against potential pathogens
- Dosing convenience and safety


Fluoroquinolone Pharmacokinetics

<table>
<thead>
<tr>
<th>Fluoroquinolone (dose)</th>
<th>Plasma C_{max} (µg/mL)</th>
<th>Prostate fluid/Plasma</th>
<th>Prostate tissue/Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin (500 mg oral)</td>
<td>2.3</td>
<td>2.26</td>
<td>1.86</td>
</tr>
<tr>
<td>Gatifloxacin (400 mg oral)</td>
<td>3.9</td>
<td>1.05–1.72</td>
<td>ND</td>
</tr>
<tr>
<td>Levofloxacin (500 mg oral)</td>
<td>5.1</td>
<td>ND</td>
<td>2.96</td>
</tr>
</tbody>
</table>


Evolving Etiology of Chronic Bacterial Prostatitis

- *E. coli* is commonly believed to be the most prevalent pathogen
- However, accumulating evidence indicates a greater role by Gram-positives
- Antibiotic treatment requires broad-spectrum activity
  - Ciprofloxacin indicated only for Gram-negative pathogens (*E. coli* and *P. mirabilis*)

### Most Common Admission Pathogens Isolated – Levo vs Cipro

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Number of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus faecalis</td>
<td>99</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>53</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus</td>
<td>41</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>39</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>26</td>
</tr>
<tr>
<td>Streptococcus mitis</td>
<td>20</td>
</tr>
<tr>
<td>Coagulase(-) staphylococci</td>
<td>19</td>
</tr>
</tbody>
</table>

Total of 499 pathogens were isolated at study entry.


### Most Common Admission Pathogens Isolated – Trovan NDA Submission

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Number of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus epidermidis</td>
<td>67</td>
</tr>
<tr>
<td>Coagulase(-) staphylococci</td>
<td>61</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus</td>
<td>40</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>35</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>32</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>30</td>
</tr>
</tbody>
</table>

Total of 391 isolates from trovafloxacin and ofloxacin treatment arms.

Trovan® (trovafloxacin) new drug application. Available at FDA website:

### Most Common Admission Pathogens Isolated – Gati vs Cipro

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Percent of Total Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus faecalis</td>
<td>40</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>21</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>11</td>
</tr>
</tbody>
</table>

Pretreatment pathogens were isolated by Monoclonal antibody technique.

Why Evolving Etiology for Chronic Bacterial Prostatitis?

- In early to mid 1990s, *E. coli* was predominant pathogen isolated
- Since ciprofloxacin approval in 1996, most CBP patients were empirically treated with an antibiotic, usually a quinolone
- Frequent use of older quinolones may have eradicated Gram-negatives, but were less effective against Gram-positives
- Newer quinolones with greater Gram-positive activity may be more effective for today’s infections


Treatment of Nonbacterial Prostatitis

Antibiotics improved symptoms in patients where bacteria were not isolated

<table>
<thead>
<tr>
<th>% Improvement</th>
<th>N</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Marked</th>
</tr>
</thead>
<tbody>
<tr>
<td>All categories</td>
<td>102</td>
<td>25.3</td>
<td>17.6</td>
<td>20.9</td>
<td>36.3</td>
</tr>
<tr>
<td>Category II</td>
<td>14</td>
<td>27.3</td>
<td>27.3</td>
<td>18.2</td>
<td>27.3</td>
</tr>
<tr>
<td>Category IIIA</td>
<td>49</td>
<td>23.3</td>
<td>11.6</td>
<td>20.9</td>
<td>44.2</td>
</tr>
<tr>
<td>Category IIIB</td>
<td>39</td>
<td>27.0</td>
<td>21.6</td>
<td>21.6</td>
<td>29.7</td>
</tr>
</tbody>
</table>


Antibiotic Clinical Success for Nonbacterial Prostatitis

Possible reasons why antibiotics are clinically effective against nonbacterial prostatitis:

- Powerful placebo effect
- Prolonged antibiotics may eradicate offending organism not cultured or thought to be nonpathogenic
  - *Chlamydia*, *Mycoplasma*, coagulase(-) staphylococci, diptheroids
- Beneficial immunological effects

Efficacy of Levofloxacin vs Ciprofloxacin for Chronic Bacterial Prostatitis

- Levofloxacin 500 mg QD (N=136)
- Ciprofloxacin 500 mg BID (N=125)

<table>
<thead>
<tr>
<th>Microbiological Response</th>
<th>Clinical Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>75.0% (95% CI [-8.98, 12.58])</td>
<td>76.8% (95% CI [-13.28, 8.87])</td>
</tr>
</tbody>
</table>


Resolution of Symptoms

<table>
<thead>
<tr>
<th>Clinical Symptoms</th>
<th>Percent Resolution of Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Clinical Success (cured and improved)</td>
<td>Levofloxacin 75.0% Ciprofloxacin 72.8%</td>
</tr>
<tr>
<td>Prostate tenderness</td>
<td>Levofloxacin 51.8% Ciprofloxacin 57.3%</td>
</tr>
<tr>
<td>Perineal tenderness</td>
<td>Levofloxacin 76.8% Ciprofloxacin 73.6%</td>
</tr>
<tr>
<td>Perineal discomfort</td>
<td>Levofloxacin 58.0% Ciprofloxacin 47.4%</td>
</tr>
<tr>
<td>Sense of incomplete voiding</td>
<td>Levofloxacin 43.8% Ciprofloxacin 36.1%</td>
</tr>
<tr>
<td>Suprapubic discomfort</td>
<td>Levofloxacin 66.7% Ciprofloxacin 48.3%</td>
</tr>
<tr>
<td>Low back pain</td>
<td>Levofloxacin 48.0% Ciprofloxacin 33.3%</td>
</tr>
</tbody>
</table>


Patient Compliance: Doses per Day

Objective:
- Review of medication compliance studies that utilized electronic monitoring as an assessment tool
  - 76 studies evaluated
- Patient compliance based on regimen:
  - QD = 79%
  - BID = 69%
  - TID = 65%
  - QID = 51%

Conclusion:
- Increased compliance with fewer daily doses