Fluoroquinolone-Use Evaluation for Acute Cystitis

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OBJECTIVE:
To determine whether clinically acceptable, less expensive medications may have been appropriate for patients prescribed a fluoroquinolone for uncomplicated acute cystitis.

DESIGN:
Fluoroquinolone overuse for treating lower, acute, uncomplicated urinary tract infections (acute cystitis) was measured through a drug-use evaluation study. According to recent guidelines developed for managed care organizations, trimethoprim/sulfamethoxazole (TMP/SMX) is the primary preferred agent and nitrofurantoin the secondarily preferred agent for treatment of acute cystitis. The DUE method consisted of reviewing randomly selected charts of women patients prescribed a fluoroquinolone to treat acute cystitis during a six-month timeframe. Patient charts were reviewed to validate the diagnosis of acute cystitis and to determine whether use of either TMP/SMX or nitrofurantoin was contraindicated.

SETTING:
A 63,000-member, staff-model health-maintenance organization in Maryland.

RESULT:
A search of the pharmacy and medical database over the period March 28 to September 29, 1994, identified 436 patients prescribed a fluoroquinolone who had a possible diagnosis of acute cystitis. From this group, 150 patients were randomly selected for chart review. Of these patients, 110 (73%) patients were confirmed to have acute cystitis. Of the acute cystitis patients, 63 (57%) had no contraindications to TMP/SMX and 96 (87%) had no contraindications to nitrofurantoin recorded in the medical record. Only six (5%) patients had contraindications to both TMP/SMX and nitrofurantoin.

CONCLUSION:
Some 95% of acute cystitis patients prescribed a fluoroquinolone had no documented contraindications to either nitrofurantoin or TMP/SMX. Prescribing clinically acceptable and less expensive therapies, such as TMP/SMX or nitrofurantoin, may reduce prescription costs for treating acute cystitis and may help reduce the development of bacterial resistance to the valuable fluoroquinolone class of drugs.

KEY WORDS:
Fluoroquinolones, Managed care, Drug-use evaluation, Prescribing guidelines, Nitrofurantoin, Trimethoprim–sulfamethoxazole, Acute cystitis.

Managed care organizations (MCOs) are striving to reduce healthcare costs while maintaining or improving healthcare quality. Drug-use evaluation (DUE) is a recognized method of reviewing medical care; it can be effectively used in MCOs. Through analyzing, understanding, and modifying practices of affiliated physicians, an MCO can balance cost containment with quality care. DUE can be an effective tool for identifying ways to reduce both drug and overall treatment costs in acute- and chronic-care situations. DUE is a method by which actual drug use can be compared with desired or ideal drug use. Discovery of physician-prescribing habits that deviate from an MCO's preferred criteria enables intervention to bring actual drug use more in line with established standards of practice.

Authors
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Columbia Medical Plan (CMP) is a 63,000-member staff-model health maintenance organization in Maryland; its two clinical sites, located in Columbia and Annapolis, are staffed by approximately 200 physicians. Anti-infective agents accounted for 8–9% of CMPs overall pharmacy budget in 1994.5

Each year, urinary tract infections (UTIs) are responsible for 6–7 million physician office visits nationally, costing about $4.5 billion.6,7 Most cases of acute cystitis occur in young women, and the most common bacterial causes in that group are Escherichia coli (80%) and Staphylococcus saprophyticus (5–15%).7

CMP adopted guidelines for treating acute cystitis (Figure 1) as one method to encourage more efficient medical service. In support of this guideline, a DUE was conducted to evaluate fluoroquinolone use for treating acute cystitis to determine if clinically acceptable, less expensive therapies, specifically trimethoprim–sulfamethoxazole (TMP/SMX) or nitrofurantoin, were indicated. By reserving fluoroquinolones for more serious infections, CMP may be able to reduce pharmacy prescription costs.

Another benefit to reducing unnecessary fluoroquinolone use is reducing the potential resistance development to this important drug class. Numerous authors have warned that extensive fluoroquinolone use raises the risk of resistance development, which has been seen with previously susceptible strains of Staphylococcus aureus and Pseudomonas aeruginosa.19–20 Many authors have concluded that fluoroquinolones should ideally be reserved for use in serious infections, while alternative drugs are indicated for less serious infections.
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Table 1. Contraindications for Nitrofurantoin and Trimethoprim–Sulfamethoxazole*  

<table>
<thead>
<tr>
<th>Nitrofurantoin</th>
<th>TMP/SMX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>Treatment failure</td>
</tr>
<tr>
<td>Glucose-6-phosphate</td>
<td>Glucose-6-phosphate</td>
</tr>
<tr>
<td>dehydrogenase deficiency</td>
<td>dehydrogenase deficiency</td>
</tr>
<tr>
<td>Anuria, oliguria, or renal impairment</td>
<td>Megoblastic anemia secondary to folate deficiency</td>
</tr>
<tr>
<td>Resistant organism</td>
<td>Resistant organism</td>
</tr>
<tr>
<td>Pregnancy at term, during labor or delivery, or when the onset of labor is imminent</td>
<td>Pregnancy at term and during nursing</td>
</tr>
<tr>
<td>Drug interactions such as required use of magnesium-based antacids, probenecid, and sulfapyrazine</td>
<td>Drug interactions such as required use of thiazides</td>
</tr>
</tbody>
</table>

*Adapted from references 23 and 24.

METHODS

The DUE design was a randomized, observational chart review of women patients who were prescribed a fluoroquinolone for acute cystitis treatment between March 28 and September 29, 1994. Based on a 95% fluoroquinolone overuse rate measured in a pilot DUE,24 we estimated that 116 evaluable encounters were needed to detect a 90% overuse rate using a one-sided 0.05 significance level with 0.80 power. Based on a 28% ineligibility rate measured in the pilot DUE, we estimated that chart review of 150 patient records would deliver about 116 evaluable encounters. Eligibility was based on the following inclusion criteria:  

▲ Woman  
▲ Age 18–70 years  
▲ Prescription for a fluoroquinolone  
▲ Uncomplicated acute cystitis confirmed upon review of medical record.

A list of possible acute cystitis encounters was obtained from the medical claims database by searching for codes 595, 595.0, 599.0, 599.7, and 599.9 as listed in International Classification of Diseases, ninth revision (ICD-9).25 These acute cystitis encounters were sorted by drug therapy, using local drug code numbers from a pharmacy benefits database printout.

Every fifth patient was selected from a randomized list of ICD-9 codes for acute cystitis matched with fluoroquinolone prescriptions. The gender, age, drug prescription, and diagnosis of patients were confirmed at the time of chart review. Men patients were replaced by the next randomly selected case number (the fifth patient after the last patient chosen in sequence). Patient charts meeting all inclusion criteria were then reviewed for possible contraindications to TMP/SMX and nitrofurantoin (Table 1). Important assumptions in this study were the following:

▲ Sufficient information was available in the chart to confirm acute cystitis diagnosis.  
▲ If no culture and sensitivity (C & S) results were recorded, the pathogens were assumed susceptible to nitrofurantoin and TMP/SMX.  
▲ If no contraindications to use of TMP/SMX or nitrofurantoin were documented in the medical records, therapy was assumed to be indicated.

Preliminary review of these 150 charts resulted in five charts being rejected because of a diagnosis other than UTI. For the remaining 145 charts, each UTI encounter was classified as acute cystitis, complicated UTI, recurrent UTI, or pyelonephritis as defined in Table 2. A total of 35 encounters were excluded from final analysis: three for age < 18 years, 11 for age > 70 years, 19 for pyelonephritis, one for complicated UTI (anatomical defect), and one for a recurrent UTI. The remaining 110 encounters were classified as acute cystitis and were included in the final analysis.

RESULTS

Based on information documented in the patient charts, six of the 110 (5%) patients treated with fluoroquinolones showed evidence of contraindications to both TMP/SMX and nitrofurantoin. In 96 of the 110 (87%) patient charts, no contraindications to nitrofurantoin were recorded. In 63 of the

Table 2. Definitions of Urinary Tract Infections

| Lower acute uncomplicated UTI (acute cystitis): An infection of the bladder with dysuria, frequency, urgency, pyuria, suprapubic discomfort, and/or clinically significant bacteruria.  
| Complicated UTI: An infection resulting from or associated with an anatomical and/or functional abnormality of the urinary tract or other predisposing factor.  
| Pyelonephritis: Infection of the kidney with flank pain, tenderness, fever, pyuria, and bacteriuria.  
| Recurrent UTI: Multiple symptomatic episodes (more than three in preceding 12 months, excluding current presentation).  
| Bacterial resistance: Bacterial resistance to either TMP/SMX and nitrofurantoin as defined by culture and sensitivity testing.  
| Treatment failure: Change in therapeutic agent because of persistent symptoms within a two-week period. |

Table 3. Frequency of Contraindications to Trimethoprim–Sulfamethoxazole and Nitrofurantoin Found in Chart Review

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>TMP/SMX</th>
<th>Nitrofurantoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy/intolerance</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Nonsusceptible pathogen</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

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▲ Recurrent UTI: Multiple symptomatic episodes (more than three in preceding 12 months, excluding current presentation).  
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Table 4. Fluoroquinolone Dose and Therapy Duration for 110 Acute Cystitis Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Total No. Patients</th>
<th>3 Days</th>
<th>5 Days</th>
<th>7 Days</th>
<th>10 Days</th>
<th>14 Days</th>
<th>21 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>250</td>
<td>60</td>
<td>1</td>
<td>10</td>
<td>24</td>
<td>22</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500</td>
<td>46</td>
<td>0</td>
<td>7</td>
<td>19</td>
<td>19</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>200</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lomefloxacin</td>
<td>400</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5. Acquisition Costs for 110 Acute Cystitis Patients Prescribed Fluoroquinolones

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Cost($)/unit dose</th>
<th>Total No. Patients</th>
<th>3 Days</th>
<th>5 Days</th>
<th>7 Days</th>
<th>10 Days</th>
<th>14 Days</th>
<th>21 Days</th>
<th>Total Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>250</td>
<td>2.705</td>
<td>60</td>
<td>16.23</td>
<td>270.50</td>
<td>908.88</td>
<td>1190.20</td>
<td>151.48</td>
<td>13.61</td>
<td>2850.90</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500</td>
<td>3.131</td>
<td>46</td>
<td>219.17</td>
<td>832.85</td>
<td>1189.78</td>
<td>87.67</td>
<td>2329.46</td>
<td></td>
<td>5147.34</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>200</td>
<td>3.057</td>
<td>2</td>
<td>30.57</td>
<td>42.80</td>
<td>73.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lomefloxacin</td>
<td>400</td>
<td>6.107</td>
<td>1</td>
<td>42.75</td>
<td>42.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400</td>
<td>2.543</td>
<td>1</td>
<td>50.86</td>
<td>50.86</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>110</td>
<td>113.36</td>
<td>13.61</td>
<td>2329.46</td>
<td>5147.34</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All listed products are indicated as twice a day (b.i.d.) therapies with the exception of Maxaquin, which is indicated as once-a-day (q.d.) therapy.
Costs were calculated using average wholesale prices from July 1995 Redbook. The referenced prices (derived from published price lists) do not reflect the actual prices paid by CMP or its members.

110 (57%) patient charts reviewed, no contraindications to TMP/SMX were recorded. Contraindications to TMP/SMX and nitrofurantoin are summarized in Table 3 for the 110 patient charts reviewed.

Information regarding the dose, frequency, and duration of therapy for each specific fluoroquinolone antibacterial therapy prescribed is in Table 4. Actual prescription costs for these 110 patients could not be calculated because of unknown patient copayment amounts and deductibles that differ based on contractual agreements between CMP and employers in their service area. However, prescription costs were estimated based on average wholesale price (AWP) of the prescribed fluoroquinolones. Table 5 summarizes the fluoroquinolone prescription cost using the dosage and length of therapy data shown in Table 4.

DISCUSSION

This study demonstrated a useful technique for conducting a statistically supported DUE at an MCO. Investigators matched pharmacy and medical claims databases to compile a complete list of patients from which a representative sample could be randomly selected. This method of patient selection avoids the potential for selection bias inherent in DUEs conducted without randomization. The results of this DUE can be considered representative of the CMP patient population.

About two months were required to collect and analyze the DUE data.

Of the 150 patients chosen for chart review, most excluded patients either had pyelonephritis or were older than 70 years. Pyelonephritis was excluded because nitrofurantoin is not indicated for this condition. Some of these pyelonephritis patients may have been appropriate for treatment with TMP/SMX. Patients older than 70 years were excluded because of the potential for renal impairment, allowing more latitude for physicians to determine the best therapy for treating the patient.

Of patients prescribed a fluoroquinolone for acute cystitis, 95% had no contraindications to either nitrofurantoin or TMP/SMX. This number may be inflated because of the difficulty in assessing medical histories based solely on retrospective chart review. In general, physicians do not extensively document their reasons for choice of empiric therapy or note pertinent negative findings. Consequently, we made several assumptions when no information was recorded regarding diagnosis, organism susceptibility, and contraindications to nitrofurantoin and TMP/SMX.

Although 22 charts were excluded from analysis because the medical record indicated a condition other than acute cystitis, some of the 110 qualifying charts may have lacked information indicating a condition other than acute cystitis. Based on the finding that only one patient had a pathogen nonsusceptible to both TMP/SMX and nitrofurantoin, we believe the C & S assumption was valid. The number of patients with contraindications to TMP/SMX and nitrofurantoin may have been underestimated because physicians did not ask about or record information specific to these two drugs.

As shown in Table 4, ciprofloxacin was the fluoro-
Fluoroquinolone prescribed almost exclusively. An interesting finding was that 44 of the 106 (42%) ciprofloxacin prescriptions consisted of more than seven days of therapy and 46 of the 106 (43%) ciprofloxacin prescriptions were for 500 mg b.i.d. This prescribing pattern for ciprofloxacin contributed to high prescription costs shown in Table 5.

Overall, we demonstrated that a fluoroquinolone prescription will rarely be the only therapeutic choice available for treating episodes of acute cystitis among CMP's patient population. The significance of these results to CMP is that about 600 patients per year may be prescribed a fluoroquinolone for acute cystitis when other, less expensive, clinically acceptable therapies may be appropriate. Considering the typically higher prescription costs and the impact of potential resistance, fluoroquinolones would be better reserved for treatment of serious infections rather than relatively minor infections such as acute cystitis.

CMP is conducting an educational intervention program to influence physicians to adopt the guidelines for the treatment of acute cystitis shown in Figure 1. Results from this intervention program will be reported to the managed care community as they become available.

CONCLUSION

This DUE demonstrated that 95% of CMP patients prescribed a fluoroquinolone for acute cystitis had no documented contraindications to nitrofurantoin or TMP/SMX. In addition, 500 mg/dose ciprofloxacin therapy was often prescribed longer than seven days. Prescribing clinically acceptable and less expensive therapies, such as TMP/SMX or nitrofurantoin, may significantly reduce prescription costs for acute cystitis and may help reduce the potential for continued bacterial resistance development to the valuable fluoroquinolone class of drugs.

References