PATIENT PRESENTATION

Pharmacists learn early in their training that any drug can cause an adverse event. As might be expected, the frequency of adverse events tends to increase in the presence of polypharmacy and in those with multiple comorbidities. Some adverse events with drug therapy are preventable and include those associated with use of the incorrect drug, incorrect dose, delayed administration of therapy, and omitted administration of therapy. It has been reported that antibiotics are the class of drugs most frequently implicated as causing adverse events (Table 1). Fortunately, most antimicrobials used in clinical practice at present are well tolerated and adverse events that do occur are generally mild, as discontinuations due to these unforeseen events are generally less than 5%.

Typical adverse events associated with antimicrobials involve pharmacokinetic interactions manifested by increases or decreases in serum concentrations, gastrointestinal events, allergic reactions, and cardiovascular events. However, pharmacists should be aware of an additional important safety concern regarding the use of antibiotics. Although not historically considered when evaluating the safety and tolerability of antimicrobial therapy, the impact of antimicrobial use on the selection of resistance should also be considered with the initiation of therapy. As a result of antimicrobial exposure(s), the use of these therapies has the potential to select for resistance in either the target pathogen (eg, *Streptococcus pneumoniae* in community-acquired respiratory tract infections [CARTIs]) if sufficient drug concentrations do not reach the site of infection or this exposure may result in the selection of resistance in organisms (eg, enteric gram-negative pathogens colonizing the gut) that were never intended to be treated. This latter concept is termed “collateral damage” and has been defined as “a term used to refer to ecological adverse effects of antibiotic therapy; namely, the selection of drug-resistant organisms and the unwanted development of colonization or infection with multidrug-resistant organisms.”

This patient case will focus on collateral damage and how the pharmacist can play a role in the prevention of this important yet commonly neglected adverse event.

PATIENT PRESENTATION

A 64-year-old Asian man presented with increased dyspnea, sputum volume, and sputum purulence over the past week. The patient was able to sleep at night only if he sat upright. He complained of productive “coughing fits” when he tried to walk some distance or carry on a conversation.

MEDICAL AND SOCIAL HISTORY

The patient quit smoking 3 years ago after smoking 1.5 packs per day for 41 years. He had a myocardial infarction at the age of 55 years. He was diagnosed with type 2 diabetes mellitus at the age of 43 years and has had mild-to-moderate chronic obstructive pulmonary disease (COPD) since age 55. The patient has had several exacerbations of COPD per year with the

| Table 1. Drug Classes Responsible for Adverse Effects |
|-----------------|------------------|
| **Drug Class**  | **Frequency**    |
| Antibiotics     | Most frequent    |
| Antitumor agents|                  |
| Anticoagulants  |                  |
| Cardiovascular agents |          |
| Anticonvulsant agents |         |
| Diabetes therapy |                  |
| Antihypertensives|                  |
| Analgesics      |                  |
| Antiasthmatics  |                  |
| Sedative-hypnotics|                |
| Antipsychotics  |                  |
| Peptic ulcer therapy |          |

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last being about 6 weeks prior to presentation. His last episode was treated with ciprofloxacin 750 mg twice daily for 10 days. The episode before that occurred approximately 9 months prior to current presentation and was treated with amoxicillin 500 mg/clavulanic acid 125 mg 3 times daily for 10 days.

**CONCOMITANT MEDICATIONS**

Concomitant medications include hydrochlorothiazide 12.5 mg/day; ramipril 10 mg/day; glyburide 5 mg/day; metformin 500 mg twice daily; enteric aspirin 81 mg/day; fluticasone propionate 250 mcg/salmeterol 50 mcg twice daily; but patient only uses as needed (prn).

**PHYSICAL EXAMINATION**

The patient is 177.8 cm and weighs 121.6 kg (body mass index 38.5 kg/m²). Hemoglobin A1c is 8.8%.

**ASSESSMENT**

The patient was diagnosed with an acute exacerbation of chronic bronchitis (AECB). The patient was treated with levofloxacin 500 mg/day for 10 days with apparent clinical resolution of AECB.

**CURRENT COMPLAINT**

Three weeks after initiating levofloxacin 500 mg/day for 10 days, the patient complains of signs and symptoms of a urinary tract infection: painful urination, blood in urine, and urgency sensation. A culture was obtained and the patient was begun on ciprofloxacin 250 mg twice daily.

**LABS**

Culture showed *Escherichia coli* that is resistant to fluoroquinolones, tetracycline, and trimethoprim/sulfamethoxazole and sensitive to nitrofurantoin.

**PHARMACIST INTERVENTION**

This patient case is a classic example of collateral damage caused by the frequent use of broad-spectrum antimicrobials to treat CARTIs. Although the antibiotics prescribed for this patient effectively treated his AECB, it also caused the patient harm in the long term by promoting the development of multidrug-resistant enteric gram-negative microorganisms. Patients who present with a prescription for a broad-spectrum antibiotic for a CARTI should be questioned about their previous antimicrobial exposure and their compliance with such regimens. The patient in this case had taken 3 broad-spectrum antimicrobials (amoxicillin/clavulanic acid, ciprofloxacin, and levofloxacin), the latter on 2 separate occasions separated by only 6 months. Prescribing physicians and pharmacists need to be aware that the use of repeated courses of broad-spectrum antimicrobials has the potential to select for resistance in a wide range of colonizing bacteria.

**COMMENTARY**

Goals of empiric antibacterial therapy of CARTIs include treating the patient and protecting the patient and community from the future development of antimicrobial resistance. In order to effectively treat the patient, relevant pathogens (*S. pneumoniae, Moraxella catarrhalis, Haemophilus influenzae*) should be covered by the antimicrobial as well as atypicals (*Legionella, Mycoplasma pneumoniae, Chlamyphila pneumoniae*) and resistant strains (such as resistant *S. pneumoniae*). Overgrowth of resistant organisms can result in a secondary infection or “superinfection” in the same patient, which is often difficult to treat, and can spread to other patients and the community, thereby contributing to an overall increase in antimicrobial resistance.

Inappropriate use of very broad-spectrum antibiotics for community-acquired infections is associated with the development of resistance in gram-negative enterics. The term collateral damage refers to the impact an antibiotic with very broad coverage may have on the development of resistance in non-respiratory, enteric gram-negative pathogens (eg, *Pseudomonas aeruginosa, Proteus mirabilis, E. coli*). The 2 classes of antibiotics that are most commonly linked to collateral damage are the cephalosporins and the quinolones (Table 2). Exposure to second- and third-generation cephalosporins has been identified as a risk factor for infection with vancomycin-resistant enterococci. Several studies have demonstrated an association between use of third-generation cephalosporins and subsequent colonization or infection with extended-spectrum beta-lactamase–producing organisms. Receipt of fluoroquinolone therapy during the month preceding admission was identified as the only risk factor for the acquisition of fluoroquinolone-resistant, gram-negative organisms in the gastrointestinal tract of hospitalized patients in a prospective cohort study. In order to limit the emer-
gence of fluoroquinolone-resistant microorganisms, the Centers for Disease Control and Prevention has stated that newer fluoroquinolones should not be used as first-line treatment of adults with community-acquired pneumonia.

Some common antibiotic regimens, such as macrolides, beta-lactams, and respiratory quinolones, are not ideally tailored for coverage of the most frequently encountered pathogens causing CARTIs (Figure).10-13 Macrolides are not indicated for resistant *S pneumoniae*. Beta-lactams lack coverage of atypical pathogens and resistant *S pneumoniae*. Quinolones have extensive coverage that extends beyond the respiratory tract and includes enteric gram-negative pathogens, such as *E coli* and *Enterobacter* spp, thus may be associated with the adverse effect of collateral damage. Telithromycin, a ketolide antibiotic, offers a targeted spectrum of activity for respiratory tract pathogens without coverage of primarily nonrespiratory gram-negative microbes.14,15

CONCLUSIONS

Appropriate management of CARTIs requires targeted therapy with antibiotics that have a tailored spectrum of activity for pathogens likely to cause respiratory tract infections. Pharmacists are in the position to assist in the selection of the most appropriate empiric antibiotic for CARTIs via several methods. Pharmacists should advocate a reduction in the use of broad-spectrum antibiotics when not necessary and educate healthcare providers about collateral damage. In addition, pharmacists are ideal for teaching patients when antibiotic therapy is not necessary, discussing compliance with prescriptions for antibiotics, and surveying antimicrobial consumption.6,7,16,17 Most of the emphasis regarding safety of antibiotic therapy has been placed on actual signs and symptoms that occur in patients taking the drug, such as gastrointestinal symptoms or rashes. The occurrence of collateral damage has traditionally been less well appreciated as an important adverse event with antimicrobial use; however, such a side effect may have far-reaching consequences for the development of resistant organisms and the development of difficult-to-treat infections in the future.

<table>
<thead>
<tr>
<th>Table 2. Summary of Potential “Collateral Damage” from Use of Cephalosporins and Quinolones</th>
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<tbody>
<tr>
<td>Class of Agent, Pathogen(s) Selected For</td>
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<tr>
<td>Third-generation cephalosporins</td>
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<tr>
<td>Vancomycin-resistant enterococci</td>
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<tr>
<td>Extended-spectrum beta-lactamase–producing <em>Klebsiella</em> species</td>
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<tr>
<td>Beta-lactam–resistant <em>Acinetobacter</em> species</td>
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<tr>
<td><em>Clostridium difficile</em></td>
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<tr>
<td>Quinolones</td>
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<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
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<tr>
<td>Quinolone-resistant gram-negative bacilli, including <em>Pseudomonas aeruginosa</em></td>
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**Figure. Targeted Spectrum of Activity**

Ketolides 1

Macrolides 2

Beta-lactams 3

RTI Quinolones 4

Collateral Damage

Typical Respiratory Pathogens

Atypical Pathogens

Resistant Strains

Primarily Non-respiratory Gram-Negative Coverage

Respiratory Coverage

RTI = respiratory tract infection.

Data from Odenholt et al;10 Lonks et al;11 Gleason;12 Neuhauser et al.13
REFERENCES


