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Pharmaceutical Care Across the Continuum

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Groups pleased that final privacy rule lacks a written consent requirement

Some details still confuse pharmacists

The privacy rule is final at last — and its elimination of the written consent requirement pleases pharmacy groups. The medical privacy regulation under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) was published in the *Federal Register* on Aug. 14. The prior written consent requirement that had been in the original final rule was "problematic in providing appropriate health care," says **Gary C. Stein**, PhD, director of federal regulatory affairs for the American Society of Health-System Pharmacists (ASHP) in Bethesda, MD.

Many health care groups seem happy with the final rule overall.

"Hospitals want patients to know and fully understand their medical privacy rights," says a statement released by the American Hospital Association in Chicago. "But no regulation should interfere with a patient's ability to get timely, effective care. The final rule strikes the right balance."

Some confusion still exists, though. An ASHP member asked Stein if hospital pharmacies are expected to discard used, labeled medication containers in a secure landfill, as they could be considered protected health information under HIPAA.

"The new final rule [p. 53,193] indicates that this would be one of the 'unintentional disclosures that could occur as a by-product of engaging in health care communications and practices.' It would seem that such an incidental use or disclosure would be permissible as long as the covered entity has applied reasonable safeguards," he said, adding that he's unsure what constitutes reasonable safeguards.

The American Pharmaceutical Association in Washington, DC, has summarized the final changes to the privacy regulation. According to the summary, the final rule:

• **Eliminates the prior written consent requirement.** Providers have "regulatory permission" to use or disclose health information for treatment, payment, and health care operations activities. Providers that choose to obtain consent have complete discretion in the process.

• **Requires that providers make a "good-faith effort" to distribute**

their Notice of Privacy Practice to patients and obtain written acknowledgment that they received it. Providers should distribute the notice no later than the date of the first service delivery. The acknowledgement must be in writing, and pharmacists are allowed to have patients sign or initial an acknowledgement in a logbook. However, the patient must be informed on the logbook of what they are acknowledging, and the acknowledgement cannot also be used as a waiver for something else, such as a waiver to consultation with a pharmacist.

If a provider cannot obtain written acknowledgement (such as in an emergency or when a patient refuses), the provider must document efforts to obtain it. The regulation also encourages providers to use a "layered" notice, which means a short notice briefly summarizing the patient's rights that is attached to the full notice containing all of the elements required by the rule.

• **Requires providers to obtain authorization for use and disclosure for marketing activities.** Marketing involves making a "communication about a product or service that encourages the recipients of the communication to purchase or use the product or service." For example, it would be considered marketing for a pharmaceutical manufacturer to offer a pharmacy payment for a list of patients with a particular condition so it can make a communication to them about its drug product. This kind of activity would require the patient's authorization.

Marketing does not include face-to-face encounters, communications involving a promotional gift of nominal value, or communications with patients involving treatment, the services of the provider, or case management or care coordination for the patient. Refill reminders, even if subsidized by a third party, are not considered marketing. Providers also may make communications about general health issues as long as they do not promote a specific product or service.

• **Creates an additional exemption for any uses or disclosures for which the provider has obtained an authorization.**

• **Allows providers to disclose health information for treatment, payment, and certain health care operation purposes of another entity.**

• **Acknowledges that incidental uses or disclosures may occur in conjunction with lawful use or disclosure of health information.** Incidental uses and disclosures are not considered a violation of the regulation as long as the provider has applied reasonable safeguards and implemented the "minimum necessary" standard. For example, providers must take reasonable efforts not to be overheard discussing patient health information, but they do not need to build a soundproof counseling area.

Authorization formats standardized

• **Requires providers to obtain authorization for use and disclosure outside of treatment, payment, and health care operations.** Providers, however, are no longer required to use different types of authorization forms. The core requirements for authorization forms are standardized into one format.

• **Clarifies that providers may disclose health information without an authorization to a person subject to FDA jurisdiction for the purpose of: collecting or reporting adverse events, tracking FDA-regulated products, enabling product recalls, or conducting post-marketing surveillance.**

• **Requires providers, upon request, to provide a record of uses and disclosures not related to treatment, payment, or health care operations or not covered by a patient authorization.** The regulation provides exceptions for incidental disclosures and disclosures made as part of a limited data set.

• **Gives providers an additional year to revise existing contracts with business associates (until April 14, 2004).** This extension only applies to existing business contracts. New business associate contracts, as well as existing contracts that must be renewed prior to April 14, 2003, must comply with the original deadline of April 14, 2003. The regulation includes sample business

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associate contract provisions. It also clarifies that covered providers are not required to monitor the actions of their business associates. However, if a covered provider is aware of a violation of the business associate contract, the provider must take steps to end the violation.

• **Eliminates the need for researchers to use multiple consent forms; they may use one form to secure consent for research activities and authorization to use or disclose health information.** This provision more closely follows requirements found in the "common rule" that governs federally funded research. The transition provisions have also been expanded to prevent needless interruption of ongoing research.

Most hospitals have until April 14, 2003, to comply with the patient privacy rule; certain small health plans have until April 14, 2004, to comply. ■

Final prescription drug discount plan unveiled

Authority to conduct program still in question

Another long-awaited regulation has been published, but the government still might lack regulatory authority to implement it.

The Centers for Medicare and Medicaid Services (CMS) has issued the final regulation for drug discount cards endorsed by Medicare. The regulation establishing the Medicare-Endorsed Prescription Drug Card Assistance Initiative was published in the *Federal Register* on Sept. 4, 2002. The regulation aims to help Medicare beneficiaries buy their prescription drugs at lower costs and obtain other pharmacy services.

The final regulation differs from the proposed one, published on March 6, 2002, in several respects, CMS says. These include:

• More information on card program features, including drug prices and generic alternatives, will be provided on the Internet at www.medicare.gov and by phone at 800-MEDICARE [(800) 633-4227].

• Card sponsors must secure manufacturer rebates or discounts on brand-name and/or generic drugs.

• Plans must provide improved access to retail pharmacies in both urban and rural areas.

• Pharmacy organizations and others have more opportunities to offer a Medicare-endorsed card program by changing the qualifying criteria related to experience and organizational capacity.

• Card sponsors can offer two program designs.

• Only programs that ensure that beneficiaries have access to stable formularies and prices will be endorsed. Card sponsors will not be able to increase drug prices or remove drugs from the approved list for the card program for periods of at least 60 days beginning on the first day of the program's operation.

• Beneficiaries will have improved privacy protection.

CMS says it expects the initiative to yield average overall savings of 10% to 13%, and possibly up to 15% — with savings of up to 25% or more on individual drugs — for a total savings for seniors of about $1.2 billion to $1.6 billion in 2004. These savings must be shared with enrollees, either directly or indirectly through pharmacies as lower prices or pharmacy services. The initiative also will promote the use of generic drugs by educating beneficiaries about generics and providing information on generic alternatives.

A federal judge found that Medicare lacked the authority to create a drug discount card program unless it either obtained congressional approval or wrote a regulation.

The question remains, however: Does the government even have the regulatory authority to conduct this program?

Pharmacy groups filed suit against the original proposal, and a federal judge in Washington, DC, issued an injunction last September that stopped the program from being implemented. The judge found that Medicare lacked the authority to create such a program unless it either obtained congressional approval or wrote a regulation. The groups argue that the evidence the government can satisfy the court's requirement is still not apparent.

CMS administrator **Tom Scully** says CMS is "not creating a new federal program" and is authorized to grant drug card sponsors the Medicare "seal of approval" as part of its "educational authority," according to press reports. He says that if the courts reject the plan again,

the administration will ask Congress to approve it.

One pharmacy group is not optimistic about CMS' chances with Congress. "Congress has not seen enough value in 'discount card' schemes to grant CMS the authority to promote these programs using the Medicare name," says **Larry Kocot**, senior vice president and general counsel of the National Association of Chain Drug Stores in Alexandria, VA.

CMS is continuing with measures to implement the program, even amid these doubts. The agency hopes to issue a request for proposals in the next few months. ■

Pharmacists can counsel women about HRT concerns

'Natural' alternatives may be just as risky

Recent news that the risks of long-term hormone replacement therapy (HRT) may exceed its benefits has alarmed many women who use HRT to treat symptoms associated with menopause.

Pharmacists should advise these patients to always consult with their prescribers before stopping drug therapy that was intended to be chronic, says **Gayle Hudgins Cochran**, PharmD, director of experiential education, School of Pharmacy & Allied Health Sciences, University of Montana, Missoula.

Beware symptom flare-ups

"While there aren't dangers such as withdrawal symptoms or other problems with suddenly stopping HRT, there could be a flare-up of perimenopausal symptoms that could be quite uncomfortable for the person," Cochran says.

The concerns about HRT relate to a July 9 announcement by the National Heart, Lung, and Blood Institute of the National Institutes of Health that it was stopping a combination conjugated equine estrogen / medroxyprogesterone acetate (Prempro) trial. The study, part of the Women's Health Initiative (WHI), was stopped more than three years early (after an average follow-up of 5.2 years) because of an increased risk of invasive breast cancer.

The trial also found that increases in coronary heart disease, stroke, and pulmonary embolism in study participants, compared to women taking placebo, exceeded the benefits of the drug. The benefits included fewer cases of hip fractures and colon cancer.

A separate WHI study is assessing the long-term use of an estrogen replacement (Premarin) in postmenopausal women who do not have a uterus. This study is ongoing because the balance of risks and benefits is not known.

Specific study findings for the estrogen plus progestin group compared to placebo include:

- 41% increase in strokes;
- 29% increase in coronary heart disease (CHD);
- a doubling of rates of venous thromboembolism;
- 22% increase in total cardiovascular disease;
- 26% increase in breast cancer;
- 37% reduction in cases of colorectal cancer;
- a one-third reduction in hip fracture rates;
- 24% reduction in total fractures;
- no difference in total mortality (of all causes).

The increased risks for cardiovascular disease and invasive breast cancer were present across racial / ethnic and age groups and were not influenced by antecedent risk status or prior disease.

The study was conducted to assess whether long-term use of the combination hormone therapy would reduce the risk of CHD in postmenopausal women. The randomized, controlled primary prevention trial involved 16,608 women ages 50 to 79 with an intact uterus. Patients either received the combination hormone replacement therapy, 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate, or placebo. The results of the study were published in the July 17 issue of the *Journal of the American Medical Association*.

A look at alternative therapies

The study did have its limitations. The trial tested only one drug regimen, and it was not designed to distinguish the effects of estrogen from those of progestin. The study did not address the short-term risks and benefits of hormones for the relief of menopausal symptoms.

More information on any benefits of HRT is also needed. "The possible benefits of the reduced incidence of colon cancer, reduction in tooth loss, reduction in macular degeneration, improvement in cognition, and reduction of Alzheimer's disease all need further scientific

study," says **Ronald Ruggiero**, PharmD, Women's Health Pharmacy Residency Project Director for the University of California - San Francisco National Center of Excellence.

In light of the study, all of a person's symptoms and risk factors need to be evaluated before a decision is made to start or continue with HRT, Hudgins says. "There are some women for whom the risks are acceptable, if they have severe perimenopausal symptoms that are relieved by HRT and have low risk for the potential cardiovascular or cancer side effects."

Some women may feel uncomfortable with the risk and want an alternative therapy. Their options for other therapies depend on the reason for which their HRT treatment was prescribed. Estrogen by itself is not a viable alternative for most women for a couple of reasons, Cochran says. One is the lack of good evidence regarding which component of HRT, estrogen or progestin, is responsible for the cardiovascular side effects. In addition, unless the woman has had a hysterectomy, unopposed estrogen by itself increases the risk for uterine cancer.

Consider non-hormonal drugs

If HRT is primarily being used for perimenopausal symptoms (such as hot flashes and vaginal dryness), patients can opt instead for non-hormonal drugs that help with hot flashes and topical (vaginal) estrogen that can help with the vaginal symptoms.

If the HRT is primarily being used for the prevention of osteoporosis, more specific drugs such as the biphosphonates (Fosamax) can be used. Also, if the HRT is primarily being used for the prevention of cardiovascular disease, the patient can use cardiac-specific drugs instead.

Turning to "natural" estrogens, soy, and herbals that contain estrogenic compounds is another alternative that may be helpful, particularly with perimenopausal symptoms, Cochran says. However, she says she doesn't think there is convincing evidence that any of these natural estrogens has fewer risks associated with it. "They generally are weaker estrogen compounds, providing weaker estrogen effects, and thus fewer estrogen side effects. If taken or used in equipotent dose to the prescription HRT, the side effects may be much the same. Plus, because the compounding or manufacturing of these products is largely unregulated, there are additional risks associated with their use."

"For patients who decide to continue HRT therapy, the current recommendation is the use of ERT or HRT at a lower dose of conjugated estrogens tablets (Premarin) 0.3 mg or its equivalent for symptoms for three to five years," Ruggiero says. Long-term use is not encouraged.

"If [women with an intact uterus] are taking the [estrogen plus progestin] combination for short-term relief of symptoms, it may be reasonable to continue, since the benefits are likely to outweigh the risks," says **Jacques Rossouw**, MD, acting director of the WHI, in a statement. "Longer-term use or use for disease prevention must be re-evaluated given the multiple adverse effects noted in WHI."

Limit use to shortest possible duration

The manufacturer of the hormone agrees in an Aug. 28 "Dear Health Care Professional Letter."

"Prempro, Premphase and Premarin are not indicated and should not be used to prevent coronary heart disease," Wyeth Pharmaceuticals notes in the letter. "The product indications remain the same. However, because of the potential increased risks of cardiovascular events, breast cancer and venous thromboembolic events, use of Prempro, Premphase and Premarin should be limited to the shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically reevaluated. When used solely for the prevention of osteoporosis, alternative treatments should be carefully considered." ■

Report finds many daily drug errors in hospitals

Most common mistakes were wrong time, omission

A new report gives discouraging news on the rate of medication errors in hospitals. The research, reported in the Sept. 9 issue of the *Archives of Internal Medicine*, found frequent medication errors, occurring at a rate of nearly one in every five doses in the typical hospital and skilled nursing facility. The percentage of errors rated potentially harmful was 7%, or more than 40 per day per 300 inpatients, on average.

"This evidence of a high rate of medication errors in many of the institutions in the sample supports the implications of the Institute of Medicine report that the medication delivery and administration systems of the nation's hospitals and skilled nursing facilities have major systems problems," the researchers write. The Institute of Medicine report said medical errors contribute to more than 1 million injuries and up to 98,000 deaths annually.

The study examined 36 institutions, including hospitals accredited by the Joint Commission on Accreditation of Healthcare Organizations, nonaccredited hospitals, and skilled nursing facilities in Georgia and Colorado. The target sample was 50 day-shift doses per nursing unit or until all doses for that medication pass were administered. Up to four different nursing units were included at each site if available, so that 200 doses per facility could have been observed.

All data were collected during 81 observation days from May 4 to Nov. 11, 1999. Medication errors were witnessed by observation and verified by a research pharmacist. An expert panel of physicians judged clinical significance.

Errors included wrong dose, unauthorized drug

In the 36 institutions, 19% of the doses were in error. The most frequent errors by category were wrong time (43%), omission (30%), wrong dose (17%), and unauthorized drug (4%). There was no significant difference between error rates in the three settings or by size. Error rates were higher in Colorado than in Georgia; researchers found the reason for this discrepancy to be unclear.

This study follows the Joint Commission's July announcement of its National Patient Safety Goals for 2003. These goals focus on confusion in identifying patients, miscommunication among caregivers, wrong-site surgery, infusion pumps, medication mix-ups, and clinical alarm systems. Joint Commission-accredited health care organizations will be evaluated next year for compliance with these standards.

The 2003 National Patient Safety Goals and Recommendations are:

• **Improving the accuracy of patient identification.** The Joint Commission recommends that organizations use at least two patient identifiers (neither to be the patient's room number) whenever taking blood samples or administering medications or blood products. Also, prior to the start of any surgical or invasive procedure, organizations should conduct a final verification process, such as a "time out," to confirm the correct patient, procedure, and site, using active communication techniques.

'Read-back' of orders recommended

• **Improving the effectiveness of communication among caregivers.** The Joint Commission recommends that organizations implement a process for taking verbal or telephone orders that requires a verification "read-back" of the complete order by the person receiving the order. In addition, organizations should standardize the abbreviations, acronyms, and symbols used throughout the organization, including a list of those not to use.

• **Improving the safety of using high-alert medications.** Health care organizations should remove concentrated electrolytes (including, but not limited to, potassium chloride, potassium phosphate, and sodium chloride >0.9%) from patient care units. They also should standardize and limit the number of drug concentrations available in the organization.

• **Eliminating wrong-site, wrong-patient, and wrong-procedure surgery.** Health care organizations should create and use a preoperative verification process, such as a checklist, to confirm that appropriate documents (e.g., medical records, imaging studies) are available. They also should implement a process to mark the surgical site and involve the patient in the marking process.

• **Improving the safety of using infusion pumps.** Health care organizations should ensure free-flow protection on all general-use and PCA intravenous infusion pumps used in the organization.

• **Improving the effectiveness of clinical alarm systems.** Finally, the Joint Commission recommends that health care organizations implement regular preventive maintenance and testing of alarm systems. They also should ensure that alarms are activated with appropriate settings and are sufficiently audible with respect to distances and competing noise within the unit.

In other Joint Commission news, the American Society of Health-System Pharmacists in Bethesda, MD, reports that the Joint Commission won't unveil its newly renamed medication-management standards until at least next spring. The standards, however, are still scheduled for implementation in January 2004. ■

NEWS BRIEFS

Drug industry fights state price controls

The Pharmaceutical Research and Manufacturers of America (PhRMA) in Washington, DC, is continuing its fight to stop state Medicaid programs that ask for rebates from prescription drug companies. In late August, the group announced that several patient organizations, such as a Michigan chapter of the National Alliance for the Mentally Ill, had joined its lawsuit, filed in U.S. District Court for the District of Columbia.

PhRMA and the patient advocacy organizations have asked the federal court to issue a preliminary injunction invalidating a program approved by the Secretary of Health and Human Services and implemented by the state of Michigan. The program restricts Medicaid beneficiaries' access to prescription drugs unless the manufacturer pays the state additional rebates beyond those required by the Medicaid program. The lawsuit also asks the court to prohibit the Secretary from approving other states' programs sharing some or all of the characteristics of the Michigan program.

The months-old Michigan program is already considered a success by organizers. Drug companies that refused to cut prices found that their market share fell as a result of the program. For example, the market share for Merck's simvastatin (Zocor) fell from 15.6% to 1.4% in Michigan, according to *The Wall Street Journal.* Merck and AstraZeneca PLC have since cut prices to be included on the program's preferred drug lists.

PhRMA still faces a big challenge to its lawsuit in the Stabenow Rx Flexibility for States Act (S. 2536), which passed the Senate by a vote of 56-43 in July. The Stabenow Medicaid Amendment ensures states have the legal right to extend Medicaid rebates and discounts for prescription drugs to non-Medicaid-eligible residents who do not have prescription drug coverage.

PhRMA argues that the Stabenow measure would put state bureaucrats, not doctors, in charge of medical decisions for Medicaid patients. In addition, lobbying groups for the mentally ill and AIDS patients want all drugs used by their patients reimbursed under Medicaid, because not all of the patients respond to the same drugs. Some health care professionals also argue that price controls artificially inflate demand of prescription drugs by shielding patients from their true market price. ▼

FDA to revamp rules for safe drug manufacturing

The Food and Drug Administration (FDA) announced a new initiative in August to enhance the regulation of pharmaceutical manufacturing and product quality.

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The initiative focuses on the FDA's Current Good Manufacturing Practice (CGMP) program and will cover veterinary and human drugs, including human biological drug products such as vaccines. It seeks to integrate quality systems and risk-management approaches into the existing programs and encourages adoption of modern and innovative manufacturing technology.

The initiative also is intended to enhance the integration of preapproval review with CGMP programs and achieve more consistent application across agency organizational components. In addition, the initiative will use existing and emerging science and analysis to ensure that limited resources are best targeted to address important quality issues, especially those associated with predicted or identifiable health risks.

The Pharmaceutical Research and Manufacturers of America, the industry's trade group, applauded the announcement, saying it will "help ensure that patients continue to benefit from timely access to high-quality pharmaceutical products manufactured according to state-of-the-art, science-based standards." Critics, however, wondered whether FDA was loosening some standards simply because it has run out of money to inspect medical factories frequently.

For more information about the initiative, see www.fda.gov/bbs/topics/news/2002/new00829.html. ■

New FDA Approvals

The following drugs have received final approval from the Food and Drug Administration (FDA):

• *Valsartan (Diovan) by Novartis Pharmaceuticals.* The FDA has approved valsartan (Diovan) to treat **heart failure** in patients who are intolerant of angiotensin-converting-enzyme inhibitors. Valsartan, an angiotensin II receptor blocker, is the first drug in its class to obtain an indication beyond hypertension.

• *1% clindamycin and 5% benzoyl peroxide topical gel (Duac) by Stiefel Laboratories.* The FDA has approved a ready-to-dispense topical gel containing 1% clindamycin and 5% benzoyl peroxide for once-daily treatment of **inflammatory acne vulgaris**.

• *Anastrozole (Arimidex) by AstraZeneca.* The FDA has approved anastrozole (Arimidex) for the adjuvant treatment of hormone-receptor positive **early breast cancer** in postmenopausal women. Anastrozole is the only hormonal drug other than tamosifen approved for this indication. The drug was originally approved in 1996 for treatment of hormone-receptor positive advanced breast cancer in postmenopausal women. In 2000, it was also approved for first-line treatment of hormone-receptor positive advanced breast cancer in postmenopausal women.

• *Escitalopram oxalate (Lexapro) by Forest Laboratories.* The FDA has approved escitalopram oxalate (Lexapro) for the treatment of **major depressive disorder**, as well as maintenance treatment for patients with major depressive disorder. Escitalopram oxalate, a selective serotonin reuptake inhibitor, is the single-isomer of citalopram HBr (Celexa). ■

DRUG CRITERIA & OUTCOMES™

Third-generation oral cephalosporin formulary evaluation

By **Jacqueline Ragusa**, PharmD candidate
Harrison School of Pharmacy
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Drugs

- Cefditoren pivoxil (Spectracef)
- Cefpodoxime proxetil (Vantin)
- Cefdinir (Omnicef)

Mechanism of action

The third-generation cephalosporins work to inhibit mucopeptide synthesis in the bacterial cell wall by binding to penicillin-binding proteins. It is this interference that produces a defective cell wall and leads to cell death.

Chemistry

Cefditoren is structurally similar to cefpodoxime and cefdinir; however, cefditoren contains a methylthiazolyl group off the C-3 position. This structure resembles first-generation cephalosporins and is thought to contribute to cefditoren's activity against gram-positive organisms. Cefditoren and cefpodoxime are formulated as prodrugs to facilitate oral use.

Pharmacokinetics

Similar to cefpodoxime proxetil, cefditoren pivoxil cannot reach maximal activity until hydrolyzed by esterases found in the intestinal lumen.

Cefditoren, cefpodoxime, and cefdinir all penetrate blister fluid, tonsil tissue, sinus tissue, and middle ear fluid. The distribution of cefdinir and cefpodoxime extends further to bronchial mucosa and epithelial lining fluid. In addition, cefpodoxime distributes to interstitial fluid, pleural fluid, lung tissue, myometrium, seminal fluid, prostatic adenoma tissue, and bile. Penetration into human cerebrospinal fluid for these agents is not known.

Cefditoren is eliminated primarily by excretion into the urine, similar to cefpodoxime and cefdinir. As shown in **Table 1, below**, cefditoren generally shares similar pharmacokinetic parameters as cefpodoxime and cefdinir.

Indications and antibacterial activity

Cefditoren exhibits broad-spectrum activity against most respiratory organisms. A comparison of the antibacterial activity for cefditoren, cefpodoxime, and cefdinir are listed in **Table 2, p. 2**. Cefpodoxime offers a broader spectrum of activity against gram-negative organisms such as *Peptostreptococcus* sp., *Acinetobacter sp.*, *Citrobacter* sp., and *Neisseria meningitidis.*

The minimum inhibitory concentrations (MICs) for all of these agents are listed in **Table 3,**

Table 1. Pharmacokinetics

	Bioavailability (%)	C_{max} (μg/ml)	Vd (L/kg)	t ½ (hr)
Cefditoren	14		0.39	1.5
100 mg dose		-		
200 mg dose		2.6		
400 mg dose		4.1		
Cefpodoxime	50		0.7-1.15	2.1-2.9
100 mg dose		1.4		
200 mg dose		2.3		
400 mg dose		3.9		
5mg/kg		2.1		
Cefdinir			0.35	1.7-1.8
300 mg dose	21	1.6		
600 mg dose	16	2.87		
7mg/kg	25	2.3		
14mg/kg	25	3.86		

Table 2. Antibacterial activity

Microorganism	Cefditoren	Cefpodoxime	Cefdinir
S. aureus	X	X	X
S. epidermidis		X	X
S. saprophyticus		X	X
S. agalactiae	X	X	X
S. pneumoniae	X	X	X
S. pyogenes	X	X	X
Streptococcus sp. (Groups C and G)	X	X	X
Viridans group Strep.	X	X	X
C. perfringens		X	X
Peptostreptococcus magnus		X	
Peptostreptococcus anaerobius		X	
Peptostreptococcus asaccharolyticus		X	X
Propionibacterium acnes			X
Acinetobacter sp.		X	
Aeromonas hydrophila		X	X
Citrobacter diversus		X	X
Citrobacter freundii		X	
E. coli	X	X	X
Fusobacterium nucleatum		X	X
Gardnerella vaginalis		X	
H. influenzae	X	X	X
H. parainfluenzae	X	X	X
K. pneumoniae	X	X	X
Klebsiella oxytoca		X	X
M. catarrhalis	X	X	X
N. gonorrhoeae	X	X	X
N. meningitides		X	
Prevotella melaninoginica		X	
P. mirabilis	X	X	X
P. multocida		X	X
P. vulgaris		X	X
Providencia rettgeri		X	X
Providenci a stuarttii		X	
Salmonella sp.		X	X
Serratia sp.		X	
Shigella sp.		X	X
Yersinia enterocolitica		X	X

p. 3. Overall, cefditoren exhibits lower MICs against gram-positive organisms than cefpodoxime and cefdinir. However, all have demonstrated activity against all of these organisms listed.

Cefditoren has not been approved for use in patients less than 12 years of age. Cefpodoxime and cefdinir are both approved for use in pediatric patients. Those as young as six months old may receive cefdinir, while those more than two months old may receive cefpodoxime.

Clinical trials

• **Acute exacerbation of chronic bronchitis (AECB):** In a double-blind multicenter study of 903 patients 12 years of age or older with AECB, patients were randomized to cefditoren 200-400 mg BID or clarithromycin 500 mg BID for 10 days.

Table 3. Susceptibility data

Organism	MIC $_{90}$ (µg/mL) Cefditoren 1[a]	Cefpodoxime 2[a]	Cefdinir 8[a]
H. influenzae	0.015	0.5	0.5
M. catarrhalis	1	0.12	0.5
S. aureus	2	2	2
S. pneumoniae	0.03	0.06	0.06
S. pyogenes	0.08	0.015	0.015

a-National Committee for Clinical Laboratory Standards limit for susceptibility

Clinical cure rates for cefditoren 200 mg BID, cefditoren 400 mg BID, and clarithromycin 500 mg BID post-therapy were 81%, 78%, and 83%, respectively. The overall eradication rates were 79% for cefditoren 200 mg BID, 78% for cefditoren 400 mg BID, and 83% for clarithromycin. The incidence of adverse events for cefditoren 200 mg, cefditoren 400 mg, and clarithromycin were 26%, 30%, and 36%, respectively. No statistically significant differences were observed in safety or efficacy issues. The investigators concluded that cefditoren is safe and effective in treating AECB.

• **Pharyngitis/tonsillitis:** Cefditoren was compared with penicillin for the treatment of pharyngitis/tonsillitis. A double-blind multicenter trial was conducted involving 1,001 patients with a diagnosis of pharyngitis or tonsillitis caused by *S. pyogenes*. The patients were randomized to cefditoren 200 mg BID x 10 days or penicillin VK 250 mg QID x 10 days. Clinical cure rates occurred in 89% of the cefditoren patients and 86% of the penicillin patients. A higher eradication rate occurred with cefditoren both at short-term follow-up (90% vs. 83%) and long-term follow-up (85% vs. 77%). This difference in efficacy could have been due to compliance, because patients were receiving penicillin VK four times a day. *S. pyogenes* is more common among pediatric patients; however, cefditoren is not approved for use in pediatrics, nor is a suspension available with this agent.

• **Uncomplicated skin and skin structure infections:** A double-blind trial compared the use of cefditoren 200 mg BID, cefditoren 400 mg BID, and cefuroxime 250 mg BID in uncomplicated skin and skin structure infections. Clinical cure rates post-therapy were 84% for both doses of cefditoren and 88% for cefuroxime. Eradication rates for cefditoren 200 mg, cefditoren 400 mg, and cefuroxime were 81%, 85%, and 85%, respectively.

Another double-blind trial involving 828 patients evaluated the use of cefditoren vs. cefadroxil. Patients were randomized to receive cefditoren 200 mg BID, cefditoren 400 mg BID, or cefadroxil 500 mg BID. Overall eradication rates for causative skin pathogens *S. aureus* and *S. pyogenes* were 87% for cefditoren 200 mg, 82% for cefditoren 400 mg, and 77% for cefadroxil. Clinical cure rates for cefditoren 200 mg, cefditoren 400 mg, and cefadroxil were 85%, 81%, and 85%, respectively.

A limit to both of the above studies is that only the abstracts are available, making it difficult to evaluate the information.

All of the trials listed above contained a large sample size and involved many centers in the United States. There are no clinical trials to date comparing cefditoren to cefdinir or cefpodoxime, but the trials listed above demonstrate cefditoren's similar efficacy and safety profiles to the other cephalosporins.

Table 4. FDA-approved indications

Indication	Cefditoren	Cefpodoxime	Cefdinir
Acute exacerbation of chronic bronchitis	X	X	X
Community-acquired pneumonia		X	X
Acute otitis media		X	X
Acute maxillary sinusitis		X	X
Pharyngitis/tonsillitis	X	X	X
Uncomplicated skin and skin structure infections	X	X	X
Uncomplicated anorectal gonococcal infections		X	
Uncomplicated urethral and cervical gonorrhea		X	
Urinary tract infection		X	

Contraindications/precautions

As with cefpodoxime and cefdinir, patients with a known allergy to cephalosporins should avoid cefditoren. Caution should be used in patients with a previous hypersensitivity to other cephalosporins or penicillins.

An additional contraindication with cefditoren is carnitine deficiency. The hydrolysis of cefditoren pivoxil results in the formation of pivalate. After multiple dosing, pivalate is absorbed and excreted as pivaloylcarnitine. This may cause a further decrease in plasma carnitine concentrations. Cefditoren is not recommended when prolonged therapy is warranted. It is likely that cefditoren will cause clinical manifestations of carnitine deficiency.

Cefditoren, cefpodoxime, and cefdinir are pregnancy category B. These antibiotics are not recommended for use in pregnant mothers unless there is a strong need. Caution should be used when these agents are administered to nursing mothers.

Drug interactions

In general, cephalosporins are associated with fewer drug interactions, because they undergo little hepatic metabolism. There are several interactions that inhibit cephalosporin absorption, particularly with cefpodoxime and cefditoren. Absorption of these two agents is dependent on pH, whereas the absorption of cefdinir is not affected by pH. Antacids and H2 antagonists should be administered at least two hours before or after cefpodoxime and cefditoren. Similar to beta-lactam antibiotics, a drug interaction may occur with probenecid. Coadministration of cefditoren and probenecid results in higher plasma concentrations of cefditoren. Iron supplements should be separated by two hours from cefdinir administration, because these agents may reduce absorption.

Adverse effects

The adverse effects associated with cefditoren are mild and commonly present as gastrointestinal (GI) disturbances. The rates of diarrhea, nausea, and abdominal pain are similar with cefpodoxime and cefditoren. Diarrhea with cefdinir has been reported in up to 15%-19% of patients. In one study, cefditoren demonstrated a higher GI side effect incidence than cefaclor.

Dosage/administration

Cefditoren pivoxil, cefpodoxime proxetil, and cefdinir are all administered orally. The absorption of cefditoren and cefpodoxime is increased when given with a high-fat meal. In contrast, a high-fat meal will decrease the rate and extent of absorption if given with cefdinir. These reductions, however, are not likely to be clinically significant, allowing for cefdinir to be taken without regard to food.

Like most cephalosporins, clearance is reduced in patients with renal dysfunction. Therefore, patients with moderate or severe renal impairment require a dosage adjustment. It is recommended that no more than 200 mg BID be administered to patients with moderate renal

Table 5. Adult dosing

	Cefditoren	Cefpodoxime	Cefdinir
Acute exacerbated chronic bronchitis	400 mg q12hr x 10d	200 mg q12hr x 10d	300 mg q12hr x 10d or 600 mg q24hr x 10d
Acute maxillary sinusitis	-	200 mg q12hr x 10d	300 mg q12hr x 10d or 600 mg q24hr x 10d
Community-acquired pneumonia	-	200 mg q12hr x 14d	300 mg q12hr x 10d
Pharyngitis/tonsillitis	200 mg q12 hr x 10d	100 mg q12hr x 5-10d	300 mg q12hr x 10d or 600 mg q24hr x 10d
Uncomplicated skin and skin-structure infection	200 mg q12hr x 10d	400mg q12hr x 7-14d	300 mg q12hr x 10d
Uncomplicated gonorrhea	-	200 mg x 1 dose	-
Anorectal gonorrhea	-	200 mg x 1 dose	-
Urinary tract infection	-	100 mg q12hr x 7d	-

Daily Cost — Huntsville (AL) Hospital

Drug regimen	Daily cost
Cefditoren 200 mg q12hr	$2.55
Cefpodoxime 200 mg q12hr	$7.24
Cefdinir 300 mg q12hr	$6.42

impairment (ClCr 30-49 mL / min / 1.73m^2) and no greater than 200 mg QD be administered to patients with severe renal impairment (ClCr <30 mL / min / 1.73m^2).

No dose adjustments are necessary for elderly patients with normal renal function or gender.

Following hemodialysis, 30% of cefditoren is removed. The appropriate dose for end-stage renal disease has not yet been determined.

Dose adjustments are not necessary in patients with hepatic impairment.

The usage of all three drugs is relatively low with patients at Huntsville (AL) Hospital.

Current automatic interchange regimen

Presently, cefditoren is not listed in the formulary. Cefpodoxime is the current interchange regimen for cefdinir based on the dosages below:

- Cefpodoxime 200 mg q12hr for:
  — Cefdinir 300 mg q12hr
  — Cefdinir 600 mg q24hr

Recommendations

Continue with cefpodoxime as the primary third-generation oral cephalosporin. Cefpodoxime is available in suspensions for pediatrics and has more approved indications when compared with cefditoren. It also offers a broader spectrum of activity against gram-negative organisms.

In consideration of a third-generation cephalosporin agent, one must consider various factors, including populations for use and other factors discussed in this evaluation. Although less expensive, the coverage cefditoren provides for many organisms is not as good as that provided by the other two drugs. Also, cefditoren is not approved for pediatric use. This newer drug has not been studied as extensively as the other two drugs, nor does it have FDA approval for the variety of indications for which the other drugs have approval. For broad-use purposes, it currently does not meet the variety of clinical needs met by cefpodoxime and cefdinir and probably

Table 6. Summary

	Cefditoren	Cefpodoxime	Cefdinir
Mechanism of action	Inhibition of PBP	Inhibition of PBP	Inhibition of PBP
Pharmacokinetics	1. Bioavaliability = 14% 2. Renal elimination	1. Bioavaliability = 50% 2. Renal elimination	1. Bioavaliability = 16-21% 2. Renal elimination
Antibacterial activity	Gram (+): Good Gram (-): Good	Gram (+): Good Gram (-): Excellent	Gram (+): Good Gram (-): Good
Indications	1. Acute exacerbated chronic bronchitis (AECB) 2. Pharyngitis/tonsillitis 3. Uncomplicated skin infections	1. AECB 2. Community-acquired pneumonia (CAP) 3. Acute otitis media (OM) 4. Acute maxillary sinusitis 5. Pharyngitis/tonsillitis 6. Uncomplicated skin infections 7. Uncomplicated anorectal gonococcal infections 8. Uncomplicated urethral and cervical gonorrhea 9. Urinary tract infection	1. AECB 2. CAP 3. OM 4. Acute maxillary sinusitis 5. Pharyngitis/tonsillitis 6. Uncomplicated skin infections
Pediatric use	No	Two months of age	Six months of age
Adverse effects	Diarrhea (11%)	Diarrhea (7%)	Diarrhea (16%)
Drug interactions	Low	Low	Low
Dosage administration	Administer with food	Administer with food	Administer without regard to food
Suspension available	No	Yes	Yes

would not be adequate as a single formulary representative of this drug group.

Although cefdinir is somewhat less expensive than cefpodoxime, its rate of GI side effects has been reported to be higher (from noncomparative clinical trials). Cefpodoxime is perhaps the strongest candidate for a single formulary representative of this group. Although cefditoren has lower MIC values of specific gram-positive organisms, cefpodoxime still offers good coverage here. Cefpodoxime, with more approved indications, offers the broadest coverage overall and has served as a valuable drug in programs focusing on early conversion of intravenous second- and third-generation cephalosporins to the oral root. Based on institutional needs, cefpodoxime or cefdinir could serve as a single formulary representative for this drug group.

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Fluoroquinolone interactions summary

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With their unique mechanism of action, relatively limited side effect profile, and clinically useful spectrum of activity, fluoroquinolones (FQs) are playing a larger role in treatment of infections. Since their discovery in the 1960s, the original nalidixic acid structure has been continually modified to improve FQ pharmacokinetic profiles and spectrum of coverage. This, coupled with the ability of the FQs to concentrate in some tissues, fluids, and cells of the immune system, has led to a dramatic increase in FQ therapy. This increased utilization involves FQ use in complex situations with multiple drugs being used to treat numerous conditions. It is in these situations that today's health care practitioner can make an impact by assuring that interactions between the FQs and the patient's concomitant drug therapy do not compromise patient outcomes. This article highlights interactions with three of the most commonly used FQs: ciprofloxacin, levofloxacin, and gatifloxacin.

The most common FQ interaction known to health care professionals involves their administration with multivalent cations. Through chelation reactions, FQs form complexes with aluminum, calcium, iron, magnesium, and zinc salts. This interaction explains the dramatic decrease in absorption when FQs are administered with antacids, didanosine, iron formulations, multivitamins, sucralfate, and foods high in calcium (e.g., ciprofloxacin can be decreased by >50%-75%). Recommendations for avoiding this interaction when any of these combinations are necessary include administering the agents four to six hours before or one to two hours after the FQ. These are especially pertinent interactions, because they can result in subtherapeutic levels of the FQ and possibly therapeutic failure.

Other interactions with the FQs are related to their hepatic inhibition of the cytochrome P450 isoenzyme 1A2 enzyme system. While ciprofloxacin and levofloxacin have varying degrees of effect on this system, gatifloxacin is the exception, with no known enzyme inhibition interactions. Ciprofloxacin tends to have more pronounced effects than does levofloxacin. Drugs that may be

Fluoroquinolone pharmacokinetics

Quinolone	% bioavailability (oral)	Time to peak serum concentration	Half-life	% excreted renally (unchanged)	% excreted fecally
Ciprofloxacin	~70	0.5-2.3h	3-5h	40-50	20-40
Levofloxacin	~99	1-2h	6-8h	87	3
Gatifloxacin	~96	1-2h	7-14h	>70	5

affected include phenytoin, theophylline, caffeine, clozapine, olanzapine, ropinirole, and warfarin. While these interactions are all theoretically possible, there is some doubt regarding the clinical significance of each in the short-term setting. Recommendations for management would include selecting another antibiotic or monitoring more closely for the increased side effects of the object drug if a FQ and one of the mentioned agents are intended to be used concomitantly. There is a significant interpatient variability with these interactions.

Drug interactions that affect the central nervous system have also been proposed with some FQ agents. FQs have been associated with an increased risk of central nervous system stimulation and possibly seizure when administered concomitantly with nonsteroidal anti-inflammatory drugs (NSAIDs) or foscarnet. While a theory involving GABA receptors has been proposed for the interaction of NSAIDs with FQs, the mechanism of the foscarnet interaction is theorized to be an additive toxicity effect. Although the incidence is rare, these combinations should be avoided when possible.

Interactions that involve renal considerations include cyclosporine and probenecid. Cyclosporine administration concomitant with FQs has resulted in elevated cyclosporine levels. Administration of probenecid with FQs has led to decreased elimination of FQs and therefore higher concentrations.

Prolongation of the QTc interval is also a concern with use of the FQs. This is represented as a class effect and should be taken into consideration during therapy. While data are lacking at this time to determine the rate of occurrence of this reaction, current recommendations state that the use of FQs with class IA and III antiarrhythmics be avoided, as well as with other drugs suspected of causing QTc prolongation.

FQ interactions causing hyper- or hypoglycemia in patients receiving antidiabetic agents are also receiving renewed interest. The gatifloxacin package insert has been changed to include this interaction in its "Warnings" section. Levofloxacin and ciprofloxacin currently mention this interaction in their "Precautions" sections. These interactions are believed to occur rarely (hypoglycemia incidence with gatifloxacin ~0.55%), but patients receiving one of the above FQs and an antidiabetic agent should have their glucose levels monitored appropriately for their individual situation.

Other drug interactions are known to occur with the FQs. However, this article only illustrates some of the more commonly recognized interactions. A table is provided below that includes other interactions not mentioned in the text; these vary in clinical significance. The text and table should not be considered a complete list of all FQ interactions.

In conclusion, the FQs are an extensively used group of antibiotics that will likely continue to be frequently utilized. However, their use in complex clinical care will continue to create situations involving drug interactions that the health care practitioner will need to evaluate and manage appropriately to provide optimal patient outcomes.

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Fluoroquinolone interactions

Interacting drug	FQ involved	Possible outcome of interaction
Antacids	Ciprofloxacin (Cipro), Levofloxacin (Levo), Gatifloxacin (Gati)	Decreased absorption can lead to subtherapeutic FQ levels.
Class Ia and III anti-arrhythmics	Levo, Gati	Additive prolongation of QTc interval could lead to arrhythmia.
Antidiabetics	Cipro, Levo, Gati	Reports of hypo- and hyperglycemia have occurred in patients receiving antidiabetic medications.
Caffeine	Cipro, Levo	Patients who ingest large amounts of caffeine may experience increased stimulatory effects.
Clozapine/olanzapine	Cipro	Some patients might experience increased sedation/orthostatic hypotension.
Cyclosporine	Cipro	Monitor cyclosporine and serum creatinine levels in transplant patients.
Diazepam	Cipro	Monitor for increased diazepam effects (sedation/ataxia).
Didanosine	Cipro, Levo, Gati	FQ absorption can be decreased to subtherapeutic levels.
Digoxin	Gati	Monitor for signs of digoxin toxicity and check level if appropriate.
Food (high fat, high calcium, e.g., milk, cheese, sardines, almonds)	Cipro, Levo, Gati	FQ absorption can be decreased to subtherapeutic levels.
Foscarnet	Cipro	Some case reports of seizure have occurred. Avoid in patients at high risk of seizure.
Iron salts	Cipro, Levo	FQ absorption can be decreased to subtherapeutic levels.
Metoprolol	Cipro	Monitor for any changes in blood pressure or cardiac function in high-risk patients.
NSAIDs	Levo, Gati	Monitor patients for any signs of CNS stimulation.
Phenytoin	Cipro, Levo	Monitor for increased phenytoin levels and observe patient for nausea, vomiting, blurred vision, slurred speech, etc.
Probenecid	Cipro, Levo, Gati	FQ concentration may be increased. Monitor for increased incidence of headache, GI upset, etc.
Ropinirole	Cipro	Ropinirole concentration may be increased. Monitor for nausea, dizziness, somnolence.
Sucralfate	Cipro, Levo, Gati	FQ absorption can be decreased to subtherapeutic levels.
Theophylline (THP)	Cipro, Levo	Monitor and adjust THP dose as necessary.
Vitamins (with elemental cations)	Cipro, Levo, Gati	FQ absorption may be decreased to subtherapeutic levels.
Warfarin	Cipro, Levo	Monitor PT/INR and adjust warfarin as necessary.
Zinc	Cipro, Levo, Gati	FQ absorption can be decreased to subtherapeutic levels.

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