

# The Prescription

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## Bugs and Drugs: Managing Antimicrobial Resistance

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Since Sir Alexander Fleming isolated penicillin from the fungus *Penicillium notatum* in 1945, antibiotics have been considered a cure-all. Pneumonia, syphilis, gonorrhea, diphtheria, scarlet fever and many wound infections that once killed indiscriminately suddenly became treatable. Only a year later in 1946, Sir Fleming cautioned “not to use penicillin unless there was a properly diagnosed reason for it to be used,” and that “the administration of too small of doses for too short a period leads to production of resistant strains of bacteria.” It was the first warning of a problem still prevalent today.

Antimicrobial resistance is the ability of a microorganism to withstand the effects of an antibiotic.<sup>1</sup> Antimicrobial resistance occurs naturally via natural selection, but is also amplified by human practices. The use of an antimicrobial for any infection, real or feared, in any dose and over any time period, forces microbes to either adapt or die in a phenomenon known as “selective pressure”.<sup>1</sup> The microbes that adapt and survive carry genes for resistance, which can be passed on to other microbes.

The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are drug inactivation, alteration of a target site, alteration of a metabolic pathway or inability of a drug to reach an active site in adequate concentrations.<sup>2</sup> One example of drug inactivation is the deactivation of Penicillin G in some penicillin-resistant bacteria through the production of  $\beta$ -lactamases. Alterations of target sites, such as penicillin binding proteins (PBP), have led to the emergence of methicillin-resistant *Staphylococcal aureus* (MRSA).

Some sulfonamide-resistant bacteria with altered metabolic pathways do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and DNA in bacteria inhibited by sulfonamides.

Instead they turn to utilizing preformed folic acid. Still, other bacteria reduce drug accumulation and concentration by decreasing cell membrane permeability or producing efflux pumps, which drive antimicrobials out of the cell.

The emergence and spreading of antimicrobial resistance are complex problems driven by several factors, many of which are linked to the misuse of antimicrobials.<sup>3</sup> Antimicrobial use is affected by the knowledge, expectations, and interactions of prescribers and patients, economic incentives, characteristics of a country’s health system and the regulatory environment.

Many aspects of the inappropriate use of antimicrobials are patient driven. For instance, some patients believe newer and more expensive medications are more efficacious than older agents. In addition to increasing healthcare costs, this perception encourages the selection of resistance to newer agents and older agents within the same drug class. Other patients may attempt to self-medicate with antimicrobials, contributing to resistance. Self-medicated antimicrobials may be unnecessary, are often inadequately dosed, or may not contain adequate amounts of active drug, especially if they are counterfeit drugs.

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# Bugs and Drugs: Managing Antimicrobial Resistance

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In many developing countries, antimicrobials are purchased in single doses and taken only until symptoms abate, which may occur before the pathogen has been eliminated.

Prescribers' perceptions regarding patient expectations and demands substantially influence prescribing practices.<sup>3</sup> Physicians can be pressured by patient expectations to prescribe antimicrobials even in the absence of appropriate indications.

Prescribing "just to be on the safe side" increases when there is diagnostic uncertainty, lack of prescriber knowledge regarding optimal diagnostic approaches, lack of opportunity for patient follow-up, or fear of possible litigation. In some cultural settings, antimicrobials given by injection are considered more efficacious than oral formulations. Such perceptions tend to be associated with the over-prescribing of broad-spectrum injectable agents when a narrow-spectrum oral agent would be more appropriate.

Patient compliance with recommended treatment is another major problem. Patients forget to take medications, interrupt their treatment when they begin to feel better, or may be unable to afford a full course, thereby creating an ideal environment for microbes to adapt rather than be killed. Fortunately, through CareLink, patients treated within University Health System may receive their antibiotics regardless of their ability to pay. In some countries, low quality antibiotics (poorly formulated or manufactured, counterfeited or expired) are still sold and used for self-medication or prophylaxis.

Antimicrobial resistance may never be completely eliminated; however, prescribers and practitioners have a responsibility to minimize their burden on antimicrobial resistance. By prescribing antimicrobials for confirmed diagnosis at optimal doses for appropriate lengths of time, prescribers can limit the development of resistance without adversely impacting patient outcomes.

## REFERENCES:

1. [www.cdc.gov](http://www.cdc.gov). Accessed July 27, 2007.
2. Sefton AM. Mechanisms of antimicrobial resistance: their clinical relevance in the new millennium. *Drugs*. 2002; 62:557-66.
3. World Health Organization. Global Strategy for Containment of Antimicrobial Resistance. Available from [http://whqlibdoc.who.int/hq/2001/WHO\\_CDS\\_CSR\\_DRS\\_2001.2.pdf](http://whqlibdoc.who.int/hq/2001/WHO_CDS_CSR_DRS_2001.2.pdf). Accessed July 27, 2007.

# The Safe and Appropriate Use of Spiriva® and Foradil® Capsules

By Elizabeth Boldt, Pharmacy Intern

The U.S. Food and Drug Administration (FDA) issued a MedWatch safety information alert and a public health advisory regarding the correct use of Spiriva® (tiotropium bromide inhalation powder) and Foradil® (formoterol fumarate inhalation powder) capsules on February 29, 2008. Reports have been made claiming patients have swallowed both the Spiriva® and Foradil® capsules, rather than placing the capsules in the inhalation devices designed for the medication.

Spiriva® is indicated for maintenance treatment of bronchospasms associated with chronic obstructive pulmonary disease (COPD). Foradil® is indicated for maintenance treatment of asthma as well as bronchoconstriction in patients with COPD. Both medications consist of a capsule dosage form containing a dry powder formulation intended for use in the inhalation device provided for that specific medication. Spiriva® is to be used with the HandiHaler®, whereas Foradil® is to be used with the Aerolizer®. To use the delivery systems, the capsules are placed in the center well of the inhalers and are pierced by pressing and releasing the buttons on the sides of the devices. The medications are dispersed into the air stream when the patients inhale through the mouthpieces and are delivered to the lungs to improve breathing in patients with asthma and/or COPD. The capsules were designed to be inhaled through these devices; therefore, neither Spiriva® nor Foradil® will treat a patient's breathing condition if the contents of a capsule are swallowed rather than inhaled. It is important to counsel patients not to ingest the capsules, in order to avoid the waste of medication and to appropriately treat the disease(s).



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# The Safe and Appropriate Use of Spiriva® and Foradil® Capsules

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In case reports regarding ingestion of capsules, few patients experienced side effects from swallowing the capsules rather than placing the capsules in the inhalation devices. According to the Spiriva® package insert, because of tiotropium's chemical structure, it is poorly absorbed from the gastrointestinal tract. In fact, oral solutions of tiotropium have an absolute bioavailability of only 2-3 percent. Therefore Pfizer, the manufacturer, boldly states that "acute intoxication by inadvertent oral ingestion of capsules is unlikely since it is not well-absorbed systemically."

The manufacturer of Foradil®, Novartis, does not address the expected effects from accidental swallowing of capsules. Absorption of formoterol fumarate following inhalation is in the gastrointestinal tract; therefore, unintended side effects may be seen more often from the inappropriate swallowing of Foradil® capsules, rather than Spiriva® capsules.

It is important patients understand how to use both the Spiriva® HandiHaler® and the Foradil® Aerolizer® inhalers appropriately. Instructions are contained in the patient information leaflets provided with both prescriptions explaining how to correctly use the respective inhalers.

When an inhaler is used inappropriately, less medicine gets to the lungs. As healthcare providers, it is imperative to take the time to demonstrate how to use these inhalers with the medications, as patients may use other types of inhalers for their disease states and can become understandably confused.

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## Tamper-Resistant Prescription Paper & Pads

Please remember to start using tamper-resistant prescription pads or paper when electronically inputting or writing prescriptions for patients. Effective April 1, 2008, the Federal Centers for Medicare & Medicaid Services (CMS) and the Texas Health & Human Services Commission (HHSC) requires providers to use tamper resistant prescription pads for all written prescriptions submitted for payment to the Vendor Drug Program (VDP) for all Texas Medicaid beneficiaries.

The UHS Pharmacy and Therapeutics Committee has determined all written and electronically processed prescriptions should be imprinted on tamper resistant paper. This policy will be enforced for all UHS patients using UHS pharmacies, regardless of the funding (CareLink patients are included).



### Metered-Dose Inhalers (MDI)

Technique
<ul style="list-style-type: none"> <li>- Remove cap and shake inhaler</li> <li>- Exhale fully</li> <li>- Hold MDI 1-2 inches in front of mouth (or insert MDI mouthpiece between lips and teeth)</li> <li>- Breathe in slowly through mouth and press down on the inhaler one time</li> <li>- Keep breathing in slowly and deeply</li> <li>- Hold breath for 10 seconds to allow medicine to go deeply to the lungs</li> <li>- Repeat puffs as directed</li> <li>- Wait at least one minute between each dose</li> </ul>
Counseling Tips
<ul style="list-style-type: none"> <li>- Slow inhalation and coordination of actuation during inhalation may be difficult</li> <li>- Patients may incorrectly stop inhalation before finishing the spray</li> <li>- Holding inhaler 1-2 inches from mouth or using a spacer increases the chances of the medication reaching the bronchial tree. The closed-mouth technique can be used if the patient has trouble.</li> <li>- MDIs containing HFA as a propellant are replacing those with CFC as the propellant</li> </ul>
Examples (bolded items are not on UHS formulary)
<ul style="list-style-type: none"> <li>- Proventil® or Ventolin® (albuterol)</li> <li>- Xopenex® (levalbuterol)</li> <li>- QVAR® (beclomethasone)</li> <li>- Flovent® (fluticasone)</li> <li>- Azmacort® (triamcinolone)</li> <li>- Atrovent® (ipratropium)</li> <li>- Combivent® (ipratropium/albuterol)</li> <li>- Symbicort® (budesonide/formoterol)</li> </ul>

### Dry Powder Inhalers (DPI)

Technique
<ul style="list-style-type: none"> <li>- Remove cap</li> <li>- Load a dose of medicine (DPI may have: a button to slide, a piece that twists until it clicks, or a chamber for medication to be placed and pierced)</li> <li>- Turn head to the side and exhale fully</li> <li>- Firmly close lips around mouthpiece</li> <li>- Take a fast, deep breath through the mouth</li> <li>- Remove inhaler from mouth and hold breath for 10 seconds</li> <li>- Exhale slowly</li> <li>- Wait at least one minute between each dose</li> </ul>
Counseling Tips
<ul style="list-style-type: none"> <li>- DPIs deliver medication in dry-powder form without the use of propellants</li> <li>- DPIs are breath-activated, eliminating the need to synchronize inhalation with actuation</li> <li>- Sufficient inspiration is needed to activate</li> <li>- Rapid inhalation promotes greater deposition in larger central airways, but may be difficult for some patients</li> <li>- Dose is lost if patient exhales through device after loading medication</li> </ul>
Examples (bolded items are not on UHS formulary)
<ul style="list-style-type: none"> <li>- Pulmicort® (budesonide)</li> <li>- Asmanex® (mometasone)</li> <li>- Flovent® Diskus® (fluticasone)</li> <li>- Serevent® Diskus® (salmeterol)</li> <li>- Advair™ Diskus® (salmeterol/fluticasone)</li> <li>- Spiriva® (tiotropium)</li> <li>- Foradil® (formoterol fumarate)</li> </ul>

#### REFERENCES:

1. MedWatch – 2008 Safety Information Alerts. Spiriva (tiotropium bromide inhalation powder) capsules and foradil (formoterol fumarate inhalation powder) capsules. US Food and Drug Administration. <http://www.fda.gov/medwatch/safety/2008/safety08.htm#Spiriva>
2. Public Health Advisory. Important information on the correct use of spiriva and foradil capsules. US Food and Drug Administration: Center for Drug Evaluation and Research. [http://www.fda.gov/cder/drug/advisory/tiopropium\\_formoterol.htm](http://www.fda.gov/cder/drug/advisory/tiopropium_formoterol.htm)
3. Drug treatments for asthma and chronic obstructive pulmonary disease that do not use chlorofluorocarbons. US Food and Drug Administration: Center for Drug Evaluation and Research. <http://www.fda.gov/cder/mdi/drugs.htm>
4. Expert panel report 3: guidelines for the diagnosis and management of asthma. U.S. Department of Health and Human Services: National Institutes of Health: National Heart, Lung, and Blood Institute. Full Report 2007.
5. Spiriva Product Information, Pfizer.
6. Foradil Product Information, Novartis.

# Insulin-Heparin Confusion in the Hospital

by Crystal Franco, Pharm.D., Pharmacy Practice Resident

The Institute for Safe Medication Practices (ISMP) has received numerous reports concerning mix-ups between heparin and insulin in several hospitals throughout the country. The consequences of such errors could be fatal and actions should be taken to prevent future events from occurring.

One example of such an error in New Jersey involved a premature baby in the neonatal ICU who was receiving a total parenteral nutrition (TPN) infusion. Six hours after starting the infusion, the baby's blood glucose measured 17 mg/dL. Despite receiving multiple boluses and an infusion of dextrose 20 percent in ½ normal saline, the NICU staff noticed that the hypoglycemic event did not resolve until the TPN infusion was discontinued. Per physician request, the remaining TPN solution was sent for analysis which revealed the formulation contained insulin, rather than the intended heparin. Similar med errors in neonates have taken place in two other states resulting in fatal outcomes. In response, the New Jersey Department of Health and Senior Services' Patient Safety Initiative released an alert and recommendations to hospitals throughout the state.

Other medication mix-ups between insulin and heparin have been reported to the ISMP and involve multiple disciplines of the healthcare staff within each institution. In 1991 an article published by Hospital Pharmacy describes two cases similar to the aforementioned in which insulin was added to TPN mixtures instead of heparin. In another occurrence, an order for heparin 500 units was entered as an order for regular insulin 500 units. Two non-diabetic patients died after receiving injections of insulin instead of heparin during a vascular catheter flush. In addition, incorrectly transcribing verbal orders may also lead to medication errors. In a cited instance, an order to resume an insulin drip was transcribed as "resume heparin drip."

Between the dates of May 7 and June 5, 2007, three patients, two of which died, at the University of Chicago Medical Center were found in comatose states with insulin levels measuring hundreds of times greater than normal. Medical center officials and police have launched an investigation to determine whether these incidences were results of accidental medication errors or cases of intentional overdoses.

How and why are these medications so commonly mixed up? First, the potential for human error exists in ordering, preparing and administering medications. The recent increase in the use of insulin infusions, and the fact that heparin and insulin are both dosed in units may be contributing to mental slip-ups.

Another factor associated with these med errors includes the similar packaging volume. Insulin and heparin are both supplied in 10 mL vials and are commonly placed in areas that are frequently used (IV hood, nurse station, medication storage carts).

The ISMP has issued recommendations to help prevent confusion between insulin and heparin during drug preparation and to help detect errors prior to patient administration.

<b>Strategies to Prevent Confusion Between Heparin and Insulin Vials During Drug Preparation</b>
Avoid storing insulin and heparin in close proximity under laminar flow IV hoods, on countertops or in drug carts.
Consider using pre-filled heparin syringes, insulin pen devices, or ordering heparin in IV solutions from vendors to avoid similar looking vials.
Add insulin to IV solutions separate from other ingredients.
Require an independent double-check of IV insulin, IV heparin, and TPN infusions prior to dispensing.
Implement bar-code scanning for drug selection. If an automated compounder is used, the bar-code scanning should be required during set-up.
<b>To Detect Errors Between Heparin and Insulin at the Point of Administration Prior to Reaching the Patient</b>
Compare the indication for heparin or insulin with diagnoses or conditions before administration.
Record verbal orders directly on order forms and read back to verify understanding and accuracy.
Require an independent double-check of IV insulin and IV heparin before administration.

# Insulin-Heparin Confusion in the Hospital

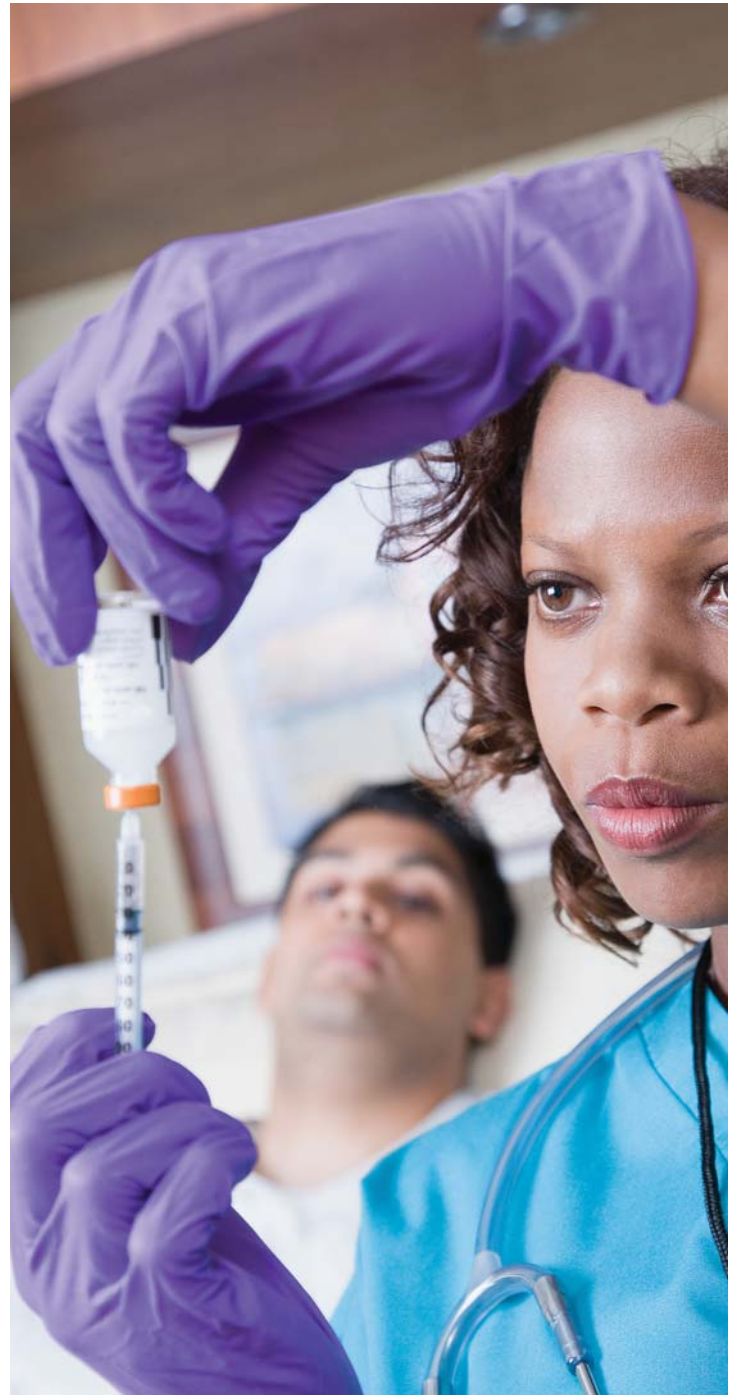
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Institutions can also consider eliminating insulin or heparin from TPN solutions and no longer using heparin as part of a vascular catheter flush procedure.

In the event of unexpected or unexplained hypoglycemic events, the ISMP recommends discontinuing all current infusions, switching them to newly prepared ones, treating the patients with dextrose, and checking for unintended additives by sending the infusions for analysis. The possibility of medication errors with oral hypoglycemic agents should also be considered.

## REFERENCES:

1. Cohen MR. Insulin overdoses that originated in the pharmacy IV admixture area. *Hosp Pharm.* 1991;26:998-9.
2. ISMP Medication Safety Alert! Action needed to prevent dangerous heparin-insulin confusion. May 3, 2007. <http://ismp.org/Newsletter/acute/acute/articles/20070503.asp>
3. Linsey Tanner Associated Press. Police probe whether patients got insulin overdoses *Chicago Sun-Times.* July 3, 2007.
4. Stokowski LA. Insulin and heparin mix-ups in neonatal intensive care. *Advances in Neonatal Care.* 2007;7:170.



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