Two unsafe practices: Administration of a product with a precipitate and reuse of a saline flush syringe

**Problem:** Two events recently brought to our attention have again thrust unsafe injection and infusion practices into the limelight. One involves the dispensing and intravenous (IV) administration of a pharmacy-prepared product despite a visible precipitate, and the other involves the reuse of prefilled saline flush syringes for multiple patients, leading to the transmission of bloodborne diseases. We have not previously published the scattered reports we have received related to these unsafe practices, initially believing they were isolated cases. However, these recent events brought to our attention that this may be a more widespread problem, which healthcare providers may need to address with clinical training programs and stepped-up monitoring to ensure adherence with safe practices.

**Dispensing and administration of a product with a visible precipitate**

To ensure the safe intravascular delivery of medications and solutions, practitioners must be observant for potentially dangerous precipitates often caused by drug or diluent incompatibilities (e.g., acid-base reactions, mixing oppositely charged organic drug ions). In an analysis of more than 300 drug incompatibilities reported to the Pennsylvania Patient Safety Authority between 2009 and 2016, almost one in five mentioned the formation of a precipitate. Precipitation reactions are usually rapid and can be observed as crystals, haziness, or turbidity. If a precipitate is observed, the drug or solution should not be administered. The precipitate can lead to therapeutic failures due to drug inactivation, catheter occlusions, and varying levels of harm due to particulate embolization, ranging from thrombophlebitis to multi-organ failure or even death. The consequences can be particularly severe in pediatric patients.

Since 1998, a total of 23 cases of precipitation have been reported to the ISMP National Medication Errors Reporting Program (ISMP MERP). In 17 cases, a pharmacist or nurse (or patient/caregiver in the home setting) noticed the precipitate and immediately remedied the problem or stopped the injection or infusion. Some of these cases involved compounding or flushing errors in which the wrong diluent, flush or base solution, or concentration/dose was used, which contributed to the formation of a precipitate. However, in 4 cases, the medication or solution was administered despite observing the precipitate.

In one of these cases, a patient with no previous cardiac or pulmonary disease died. A bag of calcium gluconate and potassium phosphate mixed in saline in the pharmacy appeared cloudy prior to administration, but the nurse still started the infusion. About an hour later, the patient was found in respiratory distress which quickly progressed to a fatal cardiac arrest. A different nurse had previously abandoned an attempt to administer the same solution due to its cloudy appearance, although she had not yet contacted the pharmacy. The nurse who then administered the solution decided to hang it after referencing a flawed hospital protocol that stated products with precipitates could be infused under “close observation” due to the risk of “sudden death.” An account of the remainder of the case is continued on page 2—Unsafe practices >
topy showed scattered pulmonary emboli, and the death was determined to be accidental and related to the infusion of the precipitated electrolyte infusion.

In the ISMP MERP database, there were two additional events in which nurses attempted to administer solutions despite observed precipitates. But fortunately, rapid IV line occlusions led to their discontinuation, although in one case, the solution was reinfused into another vein until that line also became occluded.

In 2015, ISMP learned of another event in which an 11-month-old baby received daily etoposide infusions over a 5-day period despite the presence of visible precipitates within the solution. The baby had a rare form of cancer, and four oncologists had worked together to create a custom chemotherapy treatment plan. Unfortunately, the dose of etoposide was mistranscribed as 33 mg per kg per day, instead of the correct dose of 3.3 mg per kg per day, for 5 days. The high concentration of the etoposide, which was diluted in 100 mL of normal saline, caused the drug to precipitate. Despite frequent occlusions and the need to constantly flush and reaccess the IV access port, none of the nurses reported the precipitate to a pharmacist or oncologist or stopped the infusion. Had they done so, perhaps the 10-fold dosing error could have been detected before the 5 days of therapy had been administered. When we learned of the error, the baby was being closely monitored for possible liver, renal, bone marrow, neurologic, and respiratory damage secondary to etoposide toxicity and particulate administration.

ISMP recently received another report about a compounding error with PROVAYBLUE (methylene blue) that led to precipitation of the drug and IV administration despite potentially visible particulates in the solution or IV tubing (see the Safety Brief on page 1).

**Reuse of prefilled saline flush syringes**

According to the Centers for Disease Control and Prevention (CDC), unsafe injection practices have affected more than 150,000 patients since 2001, including more than 50 documented outbreaks of viral hepatitis or bacterial infections. While many practitioners follow the CDC safe injection practices guideline, a survey of more than 5,000 practitioners about the use of needles, syringes, and vials suggests that some may be placing patients at risk for transmission of bloodborne diseases. For example, 1% of the survey respondents admitted to sometimes or always reusing a syringe for more than one patient.

We first learned about the unsafe practice of reusing a prefilled saline flush syringe from a 2013 press release issued by a New York hospital that was investigating possible disease transmission in 236 patients hospitalized during a 3-month period. In that case, a single nurse had been reusing prefilled saline syringes to flush the IV lines of multiple patients, mistakenly believing that the practice was safe. Luckily, no cases of disease transmission had been identified at the time of the press release.

More recently, the March 10, 2017, issue of Morbidity and Mortality Weekly Report (MMWR) described a very similar event, this time in a Texas hospital. A nurse who worked in a telemetry unit had been reusing prefilled saline syringes to flush the lines of multiple patients, which led to a case of hepatitis C transmission. The unsafe practice was discovered after noticing that the nurse would often leave a partially filled saline flush syringe near a computer work station. When a nurse manager investigated this practice, the nurse voluntarily reported reusing syringes during the previous 6 months, believing it was cost-effective and safe if no fluids had been withdrawn into the syringe prior to injecting the saline. The nurse had been working on the unit for 18 months but had not been taught that this was an unsafe practice by other staff members.

This is WHO’s third global patient safety challenge, following the Clean Care is Safer Care challenge focusing on handwashing in 2005, and the Safe Surgery Saves Lives challenge in 2008.

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> Unsafe practices—continued from page 2

Because all telemetry unit patients were required to have IV access, all 392 living patients potentially exposed to this unsafe practice were notified about the possible exposure to bloodborne diseases and the need for laboratory testing. One of two patients who tested positive for hepatitis C had been admitted to the unit during the same time as a patient with known preexisting chronic hepatitis C infection. Genotyping and molecular sequencing identified that both were infected with an identical strain, which accounts for only about 1% of all hepatitis C infections in the US. The CDC concluded that at least one of the hepatitis C infections was likely transmitted as a result of inappropriate reuse and sharing of the saline flushes between multiple patients.9

Safe Practice Recommendations: ISMP is concerned that the reports of IV drug administration despite observed particulates, and the reuse of prefilled saline flush syringes, are signals of more widespread unsafe practices that illustrate the need for ongoing education and stepped-up monitoring. Given the potential for harm associated with these unsafe practices, several opportunities exist to reduce the risk of errors.

Education

Provide initial orientation and annual education on injection and infusion safety, and include new and temporary nurses, pharmacists, and pharmacy technicians. Assess and reinforce practitioner competence associated with even the most basic concepts of infection control and aseptic technique, including recognition that any form of syringe and/or needle reuse is dangerous and should be prohibited. All nurses, pharmacists, and pharmacy technicians should also be taught to observe medications and solutions for precipitates, and to avoid dispensing or administering an injection or infusion if precipitates are visible or a solution that should be clear is cloudy. Provide actual examples or pictures of drugs that have precipitated10 so practitioners who have never seen this reaction know exactly what to look for.

Also, be sure practitioners understand how to identify and avoid drug incompatibilities when preparing and administering medications or solutions or flushing IV lines (e.g., thoroughly flushing the line before administering an incompatible drug, administering certain medications through a separate injection port or site). The use of an in-line filter for solutions that are prone to precipitation can also help prevent particulates from entering the body; however, precipitates can still form in the tubing below the filter, and filters may become blocked, signaling a need to investigate.2

Policies and procedures

Review organizational policies and procedures related to safe injection and infusion practices to ensure that the principles of infection control, aseptic technique, the CDC safe injection practices guideline,6 and the ISMP Safe Practice Guidelines for Adult IV Push Medications11 have been incorporated. Policies and protocols should also be very clear regarding the need to avoid or immediately discontinue any injection or infusion if particulates are observed in medications or solutions.

Surveillance

It is essential to monitor adherence with proper injection and infusion techniques in all settings where medications are prepared and administered. Consider developing a checklist12 based on the CDC safe injection practices guideline6 that can be used to conduct the surveillance process and collect the data. Syringe reuse, if identified, should be immediately corrected, and patients should always be notified of any potential exposures and the need for testing.9

References appear on page 4—Unsafe practices >

SAFETY briefs cont’d from page 2

While the daily administration of methotrexate is a well-recognized error that we have repeatedly published, it continues to happen. In the approved labeling for this drug, single oral doses of 7.5 mg once weekly are recommended for initial treatment of rheumatoid arthritis. However, divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses, given as a course once weekly, are also recommended. It appears that the use of “divided doses” is adding to the confusion. To reduce the risk of errors, the US Food and Drug Administration (FDA) should change the only approved dosing regimen in the product labeling to “once weekly as a single dose” for the treatment of rheumatoid arthritis and other non-oncologic indications, as appropriate. This would reinforce the need to program computers to default to a weekly dose, and avoid the confusing instructions on a patient’s prescription label that results when the divided dosage regimens are used. It would also be helpful for FDA to distribute a warning to health professionals to bring more attention to this ongoing problem.

As we have said many times, safety would also be enhanced if patient packs were required for methotrexate for non-oncologic use. For example, a 4-week dose pack that provides six, 2.5 mg tablets per week (15 mg), would likely have prevented the above overdose. Other weekly dosages should also be available in patient packs. When oral dosage forms are not suitable, two companies also provide methotrexate for injection in autoinjector devices. RASUVO and OTREXUP are available in multiple strengths for weekly self-injection.
> Unsafe practices—continued from page 3

References
11) ISMP ISMP safe practice guidelines for adult IV push medications. 2015. www.ismp.org/sc?id=563

> SAFETY briefs cont’d from page 3

Dangerous abbreviation—AZT. A physician ordered aztreonam for a hospitalized adult patient with human immunodeficiency virus (HIV). During order verification, an alert fired because the dose was so low at just 100 mg (usual dose 1 to 2 grams). The pharmacist became suspicious, thinking the physician most likely intended to order zidovudine. Zidovudine is sometimes dangerously referred to as “AZT” because its name was originally azidothymidine. Sure enough, entering an order for “AZT” into the hospital’s computerized prescriber order entry (CPOE) system led to both drugs appearing on the screen. Just as the pharmacist was about to call the physician for clarification, another order from the same provider came through to discontinue aztreonam and start zidovudine.

An even more dangerous situation can occur when “AZT” is confused with azathioprine. A series of incidents involving severe patient harm was reported by ISMP in the early 1990s (Cohen MR, Davis NM. AZT is a dangerous abbreviation. Am Pharm. 1992;NS329[12]:26). Although zidovudine probably isn’t used today as much as it was in the 1990s, the above incident reminds us that it is still available, and that these mix-ups are a good reason to prohibit the use of this abbreviation, including as a computer mnemonic.
One of the most important ways to prevent medication errors is to learn about problems that have occurred in other organizations and to use that information to prevent similar problems at your practice site. To promote such a process, the following selected items from the January-March 2017 issues of the ISMP Medication Safety Alert! have been prepared for leadership to use with an interdisciplinary committee or with frontline staff to stimulate discussion and action to reduce the risk of medication errors. Each item includes a brief description of the medication safety problem, a few recommendations to reduce the risk of errors, and the issue number to locate additional information. Look for our high-alert medication icon under the issue number if the agenda item involves one or more medications on the ISMP List of High-Alert Medications (www.ismp.org/sc?id=479). The Action Agenda is also available for download in a Microsoft Word format (www.ismp.org/newsletters/acute-care/articles/ActionAgenda1702.doc) that allows expansion of the columns in the table designated for organizational documentation of an assessment, actions required, and assignments for each agenda item. Continuing education credit is available for nurses at: www.ismp.org/sc?id=480.

Key: ▼ — ISMP high-alert medication

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<td>(3)</td>
<td>Despite repeated descriptions of harmful and fatal errors in publications, many organizations fail to use this information to decrease the risk of similar errors. Attribution biases that cloud the way we judge the behavior of others when errors happen often thwart our ability to learn from their mistakes. Although the Centers for Medicare &amp; Medicaid Services (CMS) requires organizations to be aware of external errors and alerts, recommended actions go unheeded by those who feel they don’t apply to them.</td>
<td>Establish a systematic way to review information about external errors and assess the organization’s vulnerability to similar errors. Identify reliable sources of information about external errors, such as ISMP newsletters and the Quarterly Action Agenda, alerts from the US Food and Drug Administration, The Joint Commission, and peer-reviewed journals. Assign a medication safety officer to review these sources to understand how and why errors happened, and determine an action plan.</td>
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<td>(4) ▼</td>
<td>Similar looking vials of ePHEdrine (Éclat Pharmaceuticals) have been mistaken as EPINEPHrine (PAR Pharmaceutical). The generic names are similar, and both vials have purple caps and purple coloring on their labels. Purple is the standard color for user-applied labels on syringes of vasopressors in the operating room (OR). Outside the OR environment, this practice leads to dangerous confusion between drugs within the same class.</td>
<td>Due to name and packaging similarities, avoid storing these vials next to each other. Take steps to differentiate the two drugs on pharmacy shelf labels and in automated dispensing cabinets. Color-coding by drug class is not recommended for commercial vial caps and labels.</td>
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<td>(4)</td>
<td>Long nonproprietary vaccine names have spurred the use of abbreviations. The Centers for Disease Control and Prevention (CDC) provides a list of standard abbreviations, but nonstandard abbreviations are used often, and some standard abbreviations are very similar, sharing a main root to identify the target disease. Mix-ups have been reported, the latest involving Hib (Haemophilus influenzae type b conjugate vaccine) and HPV (correct abbreviation was 9vHPV for human papillomavirus 9-valent vaccine, recombinant). If vaccine abbreviations are permitted, allow only current CDC-approved abbreviations to be used. Establish standard order sets or protocols that include the vaccine’s brand name (if applicable) and full nonproprietary name. If CDC-approved vaccine abbreviations are permitted in electronic formats, configure the display to allow viewing of the full nonproprietary vaccine name when hovering over the vaccine abbreviation. List full vaccine names on patient vaccination records, and provide patients with a copy.</td>
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<td>(6)</td>
<td>Organizations will be reliable only around those things that they value—safety must be one of those things. ISMP has identified two strategic initiatives related to safety that senior leaders should undertake to significantly improve reliable patient outcomes and to communicate that safety is a core value worthy of the hard work needed to achieve. Senior leaders should facilitate implementation of ISMP’s Targeted Medication Safety Best Practices, a set of interventions that address 11 medication safety issues that can cause fatal or harmful errors. As a second initiative, leaders should learn from external and internal errors, using resources such as the ISMP Quarterly Action Agenda and conducting Safety WalkRounds.</td>
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<td>More than 8 events of accidental intravenous (IV) administration of topical thrombin were reported, with the latest involving a mix-up between syringes containing IV coagulation factor and topical thrombin, which led to cardiac arrest. The vial-and-syringe packaging of some topical thrombin products makes them look like parenteral medications, and the only available human recombinant thrombin (RECOPTHROM) comes with a Luer-tip syringe. Use spray kits for topical thrombin or have the pharmacy dispense thrombin in a topical syringe so it can’t connect to an IV line. Affix warning labels to syringes and bowls of the product to warn that it should only be given topically. Separate topical thrombin vials and syringes from parenteral products both on and off the sterile field. Consider using topical thrombin in powder form or adding it to absorbable gelatin sponges.</td>
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### Mix-ups between Fresenius Kabi’s lipid emulsions, SMOFLIPID 20% (fish oil based) and INTRALIPID 20% (soy based)

**Problem:** Smoflipid, a lipid emulsion that contains fish oil, has been confused with similar-looking bags of Intralipid, a soy-based emulsion. Smoflipid had been brought into the pharmacy to familiarize staff before adding it to the formulary, and it was accidentally dispensed instead of Intralipid. The primary concern is with patients who have a fish allergy.

**Recommendation:** In order entry systems, list the products as Smoflipid (Fat Emulsion 20%) and Intralipid (Fat Emulsion 20%) instead of listing “Fat Emulsion” first. Consider including a note about the type of fat in each product (fish oil vs. soybean). Use barcode scanning to verify products, and store them in separate locations. Sequester products before they are added to the formulary.

### Inconsistent expression of strength on outsourced anesthesia syringes

**Problem:** Some outsourcing companies that dispense prefilled anesthesia medication syringes prominently display the strength on the label as the amount per mL rather than the amount per total volume. This can confuse a practitioner who is familiar with other labels that list the amount per container prominently.

**Recommendation:** Explain this issue to anesthesia staff, and have outsourcing companies correctly list the strength per total volume as the primary and prominent expression of strength, as per the USP <7> requirement for all commercially available parenterals in vials, ampuls, and prefilled syringes.

### TOPOSAR and generic etoposide injection labels with wrong strength expression

**Problem:** The labels on Toposar (Teva) and generic etoposide (Fresenius Kabi) prominently display the amount of drug per mL instead of the total amount per vial. This is not consistent with USP <7> requirements. The labeling could cause a practitioner to believe that the amount per mL is the total amount in the vial.

**Recommendation:** Place an auxiliary label on the carton and vial prominently stating the total strength per total volume. Barcode scanning during intravenous (IV) drug preparation may also help prevent an error. The US Food and Drug Administration (FDA) is investigating the label issue.

### Concomitant use of ENTRESTOPRO (sacubitril/valsartan) and angiotensin converting enzyme (ACE) inhibitors can lead to serious outcomes

**Problem:** ENTRESTOPRO should not be administered within 36 hours of switching to or from an ACE inhibitor. More than 50 cases of concomitant use have been reported to the US Food and Drug Administration (FDA), 11 of which required hospitalization due to angioedema, hyperkalemia, acute kidney injury, and hypotension.

**Recommendation:** Create order entry alerts to warn against the concomitant use of Entresto and ACE inhibitors. Conduct a thorough medication reconciliation at discharge to ensure that patients who are prescribed Entresto do not restart an ACE inhibitor upon discharge.
## Fatal route of administration recommended in journal

Fatal route of administration recommended in journal

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<td>(1, 3)</td>
<td>Intrathecal vinCRISistine was listed as a possible treatment option for leptomeningeal multiple myeloma in an article published by <em>Hematological Oncology</em>. A similar error listing the intrathecal route with vinCRISistine occurred in a 2017 article in the <em>Journal of Applied Hematology</em>. Giving vinCRISistine via the intrathecal route is fatal.</td>
<td>Mistakes can be made even in respected peer-reviewed publications, so don’t immediately accept everything you read. To keep abreast of any articles with serious errors that are retracted by journals after publication, subscribe to Retraction Watch’s blog (<a href="http://www.retractionwatch.com">www.retractionwatch.com</a>).</td>
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## Educate fluorouracil home infusion patients about accidental overinfusion

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<td>A physician prescribed a 7-day continuous infusion of fluorouracil for a patient at home via an elastomeric infusion pump. The patient received the entire infusion in just 4 days but waited until his scheduled doctor’s appointment 4 days later to report the mishap. The patient experienced serious sequelae and was admitted to the hospital for 7 days.</td>
<td>Educate patients with ambulatory infusion pumps about how the pump works, what to expect during treatment, the infusion rate, how long the infusion should last, how much should be left in the container each day, and to immediately report any incident to their care team should the container empty sooner than anticipated so an antidote can be administered.</td>
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## Use EPINEPhrine autoinjectors for anaphylaxis management

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<td>(2, 3)</td>
<td>An emergency department physician ordered EPINEPhrine 1 mg intramuscularly (IM) for a patient with anaphylaxis, which exceeds the usual anaphylaxis dose (0.2-0.5 mg). The dose was prepared and administered using a vial and syringe, leading to hypertension, tachycardia, and agitation.</td>
<td>Reconsider use of EPINEPhrine autoinjectors to deliver doses for anaphylaxis. They are now available in a generic form at a lower cost. If using vials or ampuls, prepare kits containing a 1 mg vial or ampul along with a syringe, needle, and a label listing the dose and an “IM use only” warning. Contrary to some misguided efforts to reduce the risk of administering the full contents of the 1 mg (1 mL) vial, DO NOT use a 30 or 50 unit capacity insulin syringe in the kits, as these syringes only measure in units, have an attached needle of insufficient length, and may be mistaken as a syringe containing insulin.</td>
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