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ISMP
An ECRI Affiliate

Acute Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

Guardians of grafts: Reducing medication errors in transplant recipients

Problem: Patients who have received a solid organ transplant or allogeneic (from a donor) hematopoietic stem cell transplants typically need to take lifelong immunosuppressant agents to prevent transplant rejection and graft-versus-host disease. Immunosuppressants often have a narrow therapeutic index, meaning that small differences in dose or blood concentration may lead to serious therapeutic failures or adverse drug reactions (ADRs). Dosages need to be individualized to the type of transplant, target blood concentration, body weight, drug-drug and drug-food interactions, and the risk of rejection or toxicity.[1]

Transplant recipients have highly complex needs that require well-coordinated healthcare delivery throughout the pre-, intra-, and post-transplant phases. Recipients are often prescribed multiple medications from various healthcare practitioners in highly specialized fields. However, these medications are metabolized through common pathways, making them prone to drug-drug interactions that may result in toxicity or inadequate immunosuppression. Medication dynamics such as time dependency, route, therapeutic equivalency, and ADRs also play critical roles in maintaining adequate immunosuppression without incurring undue toxicity. As the number of patients receiving transplants has been increasing, hospitals must be prepared to address these nuances.

ISMP analyzed 520 transplant medication-related errors reported to the ***ECRI and the Institute for Safe Medication Practices Patient Safety Organization (ECRI/ISMP PSO)*** (www.ismp.org/ext/591) between January 2020 and September 2023 to identify common themes and capture reports classified as mild or above, according to the Agency for Healthcare Research and Quality (AHRQ) harm scale (www.ismp.org/ext/1290). The qualitative review included categorizing the event descriptions to effectively analyze trends in the reports. The analysis identified the top prescribed medications used for post-transplant patients, which included agents that have immunosuppressant activity (72%) with tacrolimus in various formulations representing most of the errors (62%). Most cases were reported as mild harm (90%), followed by moderate harm (9%), and others (1%). The most frequent medication errors were associated with the wrong time (26%), omission (17%), and improper dose/quantity (13%). Common themes were identified with examples provided below.

Held, Suspended, or Temporarily Stopped Medication Orders

The most common theme in all event types analyzed was related to holding, suspending, or temporarily stopping immunosuppressants (13%) based on patient clinical need, which is a common requirement during transplant patient care. However, if the electronic health record (EHR) workflow and policy for holding medications has not been carefully coordinated, errors can occur. For instance, practitioners may have different interpretations regarding the actions required to place an order on hold, and how and when the medication is intended to be restarted. Additionally, instructions to hold a medication might not be easily visible to nurses viewing the medication administration record (MAR).

A prescriber provided a verbal order to a nurse to hold a patient's tacrolimus dose due to an elevated (potentially toxic) blood level. However, the MAR did not reflect this change. The hold was also not communicated to the nurse during change-of-shift. Since the order was still active on the

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HIGH-ALERT

Look-alike vials of Adrenalin and Retacrit. A prescriber ordered **RETACRIT** (epoetin alfa-epbx) to treat a patient's anemia. The pharmacy dispensed a similar-looking vial of **ADRENALIN** (**EPINEPH**rine) in error. The nurse prepared a dose from the vial she thought was Retacrit and identified the error during barcode scanning prior to administration. The 1 mg/mL vials of Adrenalin (made by Par Pharmaceutical) and 10,000 units/mL vials of Retacrit (made by Pfizer) are the same size and both have purple caps (**Figure 1**).

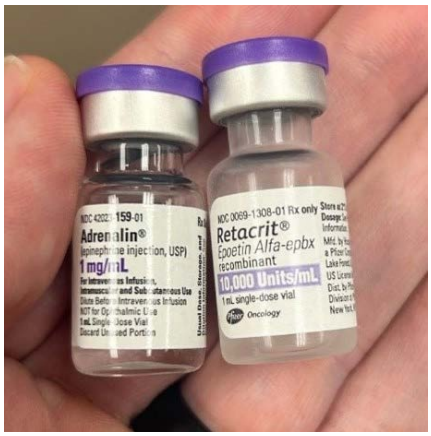

Figure 1. Adrenalin (left) and Retacrit (right) vials look similar and have purple caps.

During the event investigation, it was discovered that Adrenalin vials had been mistakenly stocked in the refrigerator with Retacrit. The pharmacy mentioned that the medications are normally stored separately. Adrenalin vials are kept on shelves at room temperature and Retacrit is stored in the refrigerator. Barcode scanning is required when medications are being stocked in most areas in their pharmacy, but it has not yet been implemented for refrigerated medications.

If your organization purchases these products, notify staff of this risk, and take steps to minimize mix-ups. Use barcode scanning when stocking, dispensing,

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patient's profile and not knowing it should be held, the pharmacy dispensed a dose, and the nurse administered the medication. The prescriber later identified that the tacrolimus should have been held and then suspended the order in the EHR, which removed the task from the MAR.

Transitions of Care/Medication Reconciliation

One in ten (10%) events reported were related to transitions of care and medication reconciliation, which are particularly challenging for organizations to manage for transplant recipients. Ineffective medication reconciliation during transitions of care may contribute to medication omissions, duplications, and other discrepancies in medication regimens.

A patient's home medication list had "mycophenolate 180 mg, take 1 tablet twice daily" documented as an active medication. However, the prescriber inadvertently omitted mycophenolate when completing the admission medication reconciliation. Three days later, a pharmacist met with the patient to review their home medication regimen and identified that the patient had been taking 3 of the 180 mg mycophenolate tablets (540 mg), twice daily prior to admission. The pharmacist notified the prescriber about the patient-reported dose of 3 tablets, and that the medication had been omitted, and the medication was restarted.

Formulation and Route Selection

One in ten (10%) events reported involved use of the incorrect transplant medication formulation or route of administration. Mix-ups between tacrolimus formulations were frequently observed, reflecting a common error type among the many drugs available in both conventional (e.g., immediate-release) and modified (e.g., delayed-release, extended-release) formulations. In addition, some drug references include off-label information about sublingual administration of the immediate-release tacrolimus formulation at approximately 50% of the oral dose for patients unable to take oral medications. This requires dose adjustments when transitioning from one route to another, which was another source of error.

*A patient was taking **ENVARSUS XR** (tacrolimus 24-hour extended-release) 6 mg daily during the hospital admission. However, the prescriber inadvertently ordered the immediate-release formulation to take once daily instead of twice daily as a discharge prescription, resulting in a subtherapeutic dose at home.*

A nurse notified a prescriber that a patient could no longer take oral medications. The prescriber updated the patient's tacrolimus order from the oral to sublingual route, but did not decrease the dose, resulting in tacrolimus toxicity.

Laboratory Monitoring

Errors associated with coordination between laboratory specimen collection and dose administration was a contributing factor in 10% of the events, which can result in inaccurate laboratory values or result interpretation that contribute to inappropriate doses, and/or prolonged hospitalization. Immunosuppressants often have a narrow therapeutic index which necessitates regular laboratory monitoring to ensure they are working effectively while limiting toxicity.

A prescriber ordered a mycophenolate mofetil level to be drawn 2 hours after the medication dose was administered. This was completed; however, the results were reported as a trough level, which led to a concern that the patient must have had an elevated level, so the prescriber discontinued the medication. A pharmacist was reviewing the patient's profile and identified the error in interpretation after the patient had missed two doses of medication. The prescriber was notified, and the medication was resumed.

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and prior to administration. To prevent misidentifying medications by viewing only the vial caps, avoid storing injectable medication vials in an upright position, especially when stored in a bin or drawer below eye level. Store them in a way that always keeps their labels visible. Consider purchasing one of these medications from a different manufacturer, if possible.

Demo product found in a code cart tray. When replenishing medications in a returned code cart, a pharmacy technician used radio frequency identification (RFID) technology and identified an unopened box labeled "DEMO DOSE 8.4% SODIM BICARB Injection, USP" (**Figure 1**). Nurses had purchased the demonstration (demo) product, distributed by Pocket Nurse, to use during code simulations on the patient care unit. Despite the box having a national drug code (NDC) and scannable barcode, the product was not recognized by RFID as 8.4% sodium bicarbonate and did not have an RFID label applied. Fortunately, the technology helped prevent this error from reaching a patient. The technician sequestered the demo product, and the issue was escalated to pharmacy leadership. These demo products are now prohibited from being used in the reporting hospital.

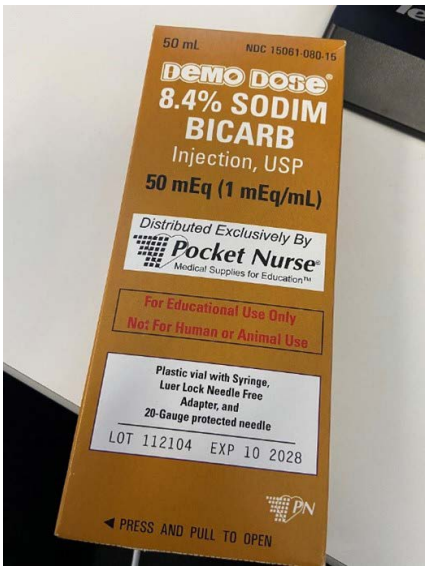

Figure 1. A demo product labeled "DEMO DOSE 8.4% SODIM BICARB Injection, USP" was mistaken for actual medication and placed in a code cart.

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Safe Practice Recommendations: The complexity of transplant medication regimens calls for a coordinated approach. Based on the ECRI/ISMP PSO data analysis, organizations should review our previous publication, *Multifactorial causes of tacrolimus errors: confusion with strength/ formulation, look-alike names, preparation errors, and more* (www.ismp.org/node/182) and consider the following recommendations to prevent patient harm.

Develop transplant order sets. Build transplant medication order sets to guide prescribers in selecting appropriate immunosuppressant doses, routes, frequencies, and formulations in accordance with the patient's clinical state (e.g., pre-, intra-, or post-procedural phase of transplant care; type of transplant; weight). Display the brand name of tacrolimus extended-release formulations on medication ordering and verification screens to help differentiate them from immediate-release tacrolimus. Automatically link products to the corresponding order sentences. Order sets should include standard times for laboratory monitoring, including the timing for measuring the target blood concentrations when applicable. Regularly review order sets and update as needed.

Use clinical decision support (CDS). Implement dose range checking based on patient parameters (e.g., weight, renal impairment). Employ drug-drug and drug-disease interaction screening. Alert prescribers when laboratory results are out of range and ensure results are available to adjust doses.

Highlight medication reconciliation safety. Evaluate the medication reconciliation process as it relates to transplant medication orders during transitions of care. Organizations must have a formal process outlining the designated prescriber responsible for completing medication reconciliation during transitions of care (e.g., admission, transfer, discharge). Document what time the medication is typically administered along with the last time it was given. When possible, confirm medication dosing from external sources (e.g., outpatient fill data, transplant clinic notes) with the patient, as dosing may be titrated based on aforementioned lab value monitoring, and the regimen taken by the patient may differ from pharmacy fill data.

Evaluate EHR hold and resume functionality. Understand the various ways that immunosuppressants can be temporarily placed on hold and resumed in your EHR system and standardize the process. "Hold" orders should be visible to all practitioners, on all medication lists, and the MAR, and should clearly indicate how long the medication is on hold (e.g., number of doses, number of days) if known. Avoid verbal orders to hold a medication. For additional recommendations, review our previous publication, *Temporarily holding medication orders safely in order to prevent patient harm* (www.ismp.org/node/103406). For additional recommendations, see ISMP ***Targeted Medication Safety Best Practices for Hospitals*** (www.ismp.org/node/160) *Best Practice #21*.

Monitor patients using an interdisciplinary approach. Conduct interdisciplinary team rounding during which the team (e.g., prescribers, pharmacists, nurses, transplant coordinators) discusses the medications for each transplant patient. Rounding with an interdisciplinary team to discuss the care of a patient in real time can be a valuable tool that detects errors and improves quality and safety. Encourage prescribers, pharmacists, and nurses to conduct a daily review of their patients' immunosuppressant medication orders (e.g., active, held, discontinued), laboratory monitoring (e.g., trough level, dose adjustment based on level), and assess for side effects. Consider building this information into a dashboard to identify patients with potential medication safety issues.[1]

Educate practitioners. During orientation and annual competency assessments, educate practitioners who may prescribe, dispense, or administer immunosuppressants about the various formulations and monitoring recommendations. Ensure practitioners understand the risk of harm associated with inappropriately timed laboratory levels, missed doses, duplicate doses, and wrong formulations, as well as the best workflow to reduce the risk of these types of errors. Review common drug-drug and drug-food interactions and what to do if they receive an alert. Alerts that were bypassed by prescribers must be flagged and followed up by a pharmacist.

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We have previously shared reports involving demo products, including in our August 10, 2023 article, *Ryanodex demo carton and vial look too much like the real thing* (www.ismp.org/node/92046). The manufacturers should package the demo products to look distinctly different than the actual product and they should not have a scannable barcode. These demo products should only be purchased by schools, teaching facilities, or staff educators. Ensure demo products used in simulation training are stored separately from medications such as in a classroom/ training area and not in patient care areas. These should never be ordered by pharmacy or brought anywhere near a pharmacy where students, technicians, or new pharmacists might get confused by them. Educators need to account for every demo product used during training. If you suspect that any training products may have been administered to a patient, please report it to the US Food and Drug Administration (FDA) and ISMP, even if the event did not harm a patient. We have notified the FDA of this issue.

Special Announcements

Survey on new Best Practices

Please complete our brief survey on the current level of implementation of the new *Best Practices* for hospitals by **April 19, 2024**. Go to: www.ismp.org/ext/1323.

ASHP free webinar series

The American Society of Health-System Pharmacists (ASHP) is offering a **FREE** webinar, ***Elevating Compliance: Navigating USP <797> with Technology and Standardization***, on **April 9, 2024**. Speakers will describe how to perform a gap analysis and identify opportunities to improve intravenous (IV) compounding safety in institutions of any size. Continuing education (CE) credit is available for pharmacists and technicians. For more information and to register, please visit: www.ismp.org/node/125713. Stay tuned for more information on opportunities to have faculty answer your questions during ***Frontline Conversations***, to be held **May 15 and 30, 2024**.

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Educate patients. In addition to asking about immunosuppressant therapy during the medication reconciliation process, educate patients to proactively maintain a current medication list that includes doses, routes, frequencies, and formulations for each drug. During transitions of care, inform patients which medications are being initiated, continued, discontinued, or adjusted, including those that are being held or reduced, for how long, and why. Teach patients what to do if they miss a dose, and signs and symptoms of ADRs that they should report to their prescriber. Encourage patients to use one pharmacy to obtain all of their medications, if possible. Other tools to consider include a medication calendar or a weekly pill organizer (designed with child-resistant features) to help with adherence.

Learn from errors. Review internally reported immunosuppressant-related errors as well as published external events, such as those described in this newsletter. Encourage staff to report close calls and errors that have reached the patient.

Reference

1) Hall CL, Fominaya CE, Gebregziabher M, Milfred-LaForest SK, Rife KM, Taber DJ. Improving transplant medication safety through a technology and pharmacist intervention (ISTEP): protocol for a cluster randomized controlled trial. *JMIR Res Protoc.* 2019;8(10):e13821.

Patient found unresponsive after Zosyn label placed on Myxredlin bag was infused

A prescriber ordered **ZOSYN** (piperacillin and tazobactam) 4.5 g/100 mL injection bags intravenously every 8 hours for a patient. The pharmacy inadvertently dispensed a **MYXREDLIN** (insulin human) 100 units/100 mL bag. Both products are made by Baxter; have the same red, white, and black colors; and are packaged in 100 mL bags (**Figure 1**). The pharmacy had a dispensing system with barcode scanning technology which alerted the pharmacy technician upon scanning that it was the incorrect medication. The technician saw the warning and scanned the correct product (Zosyn), but did not remove the Myxredlin bag from the preparation area, and placed the Zosyn label on the Myxredlin bag. This was not caught during the pharmacist check. The nurse scanned the pharmacy-generated barcode on the Zosyn label, rather than the manufacturer barcode, and unknowingly infused Myxredlin for approximately 4 hours. The patient was found unresponsive and was transferred to the intensive care unit. After reviewing the infusion bags, the nurse found that the Zosyn label had been placed on the Myxredlin bag. A hypoglycemic protocol was initiated, and the patient recovered shortly after. The organization has reached out to its electronic health record (EHR) vendor to suggest a software change that would prevent nurses from being able to scan the pharmacy-generated barcode, to facilitate scanning the manufacturer barcode.

Figure 1. Similar-looking infusion bags of Zosyn (left), and Myxredlin (right), made by Baxter.

In another hospital, a pharmacy technician had just gone through organizational medication safety training which included assessing new products for safety concerns. The technician was evaluating a new product, Myxredlin, which had recently been purchased. He noted that the Myxredlin bag looks very similar to Zosyn injection bags and escalated this concern to pharmacy leadership. The hospital has decided to store the insulin bags in a separate and secure location, flagged with auxiliary warning labels, and only plans to dispense them to defined areas where staff have received education. This was a great example of completing a safety analysis to proactively consider product characteristics that might lead to medication errors and devise a mitigation plan to proactively prevent errors from occurring.

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> **Zosyn and Myxredlin** — cont'd from bottom left

We contacted the US Food and Drug Administration (FDA) and the manufacturer and recommended altering the infusion bag labels, (e.g., using color differentiation). When the pharmacy receives a new product (e.g., new product added to formulary, drug shortage), conduct a review to identify potential risks with the product's design including look-alike labeling and packaging concerns with other products in use within the organization (www.ismp.org/node/71460). When problems are recognized, consider purchasing the product (or one product of a problematic pair) from a different manufacturer. Use barcode scanning when receiving, dispensing, filling the automated dispensing cabinet (ADC), and prior to administration. When available, practitioners should scan the manufacturer's barcode printed directly on the product. This ensures the right (or wrong as in the case described earlier) container is in hand to prevent the risk of a false positive barcode scan from just a pharmacy-applied label. Consider completing a failure modes and effects analysis (FMEA) to determine if it is possible to remove the pharmacy-generated barcode from products that contain a manufacturer barcode, to force scanning of the actual product Store look-alike products separately, and consider the use of signage, shelf talkers, or other warnings such as auxiliary labels on the infusion bags and in storage locations.

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