Clinical and economic burden of managing refrigerated medications in United States hospitals

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Introduction

Refrigerated medications represent some of the most clinically necessary, complex and costly medications available. Several guidelines and recommendations exist for their management and storage, however challenges with real-world practice may further complicate their management. Medical-grade refrigerator adoption is reported to range from 73 to 94%.[1] Adoption is projected to increase 39% *(central pharmacy)* and 50% *(point of care [POC])*, over the next 3 years *(2017 – 2020)*.[2] While medical-grade refrigerators are recommended, proper implementation and use of this technology is also of critical importance, including *(adapted from Henney, 2018)*[3]:

- Number and location deployed across healthcare system
- Dimensions and design of refrigerator
- Temperature monitor tracking
- Appropriate documentation
- Accurate alarm management
- Supporting policies and procedures
- Staff training; cold chain procedures, refrigerator use and maintenance

Refrigerated medication management may be further complicated by national drug shortage concerns.[4] Vaccines and expensive products appear to be disproportionally impacted in the shortage crisis.[5] While drug manufacturers offer some details on storage recommendations for individual medications, unfortunately few practice guidelines and standards are available. Considering practice variance in managing ambient versus refrigerated medications is key to understanding impacts to management and care. This study's purpose is to assess the clinical and economic burden of managing refrigerated medications within the acute U.S. healthcare system.

Methods

A literature review was conducted in PubMed, Embase and Google. Evidence in English language publications from 2007 – 2018 and abstracts published from ASHP from 2012 – 2018 were screened. Additionally, grey literature was searched using Google for relevant white papers, newspaper articles and reports. Inclusion and exclusion criteria were set to identify direct evidence on hospital pharmacy and POC management of refrigerated medications.

Results

Several themes were identified from our literature analysis. The following results summarize the key evidence on these themes, including: medication management for refrigerated medications, safety consequences from challenges with refrigerated medication storage, diversion of high-cost refrigerated medications, implementation challenges with refrigeration technology and resulting associated costs.

Medication management

- Refrigerated medication management across a healthcare system may be complicated by disparate technologies and complicated policies *(e.g., disparate ambient versus refrigerated medication workflows, short-dating, unit- or patient-specific requirements)*.[6]
- Sources for storage recommendations are varied and have inconsistencies.[7]
  - Pharmacists reconcile manufacturing recommendations with other resources *(e.g., USP and Trissel's Stability of Compounded Formulations)* with up-to-date peer-reviewed evidence to inform hospital pharmacy policies and procedures.
  - Victor Cohen from Maimonides Medical Center, Brooklyn, NY published efforts to consolidate up-to-date storage recommendations for their **89** medications; this required contacting **44** manufacturers directly.[7]
  - These evaluations may need to be updated with formulary changes.
- Out-of-range temperature excursions and alarm management challenges:
  - Review articles report below temperature storage events range from **24** to **89%** of cases.[8]
  - Temperature tracking devices may either be initially integrated or retrofitted, and then need proper configuration to ensure minimization of nuisance alarm excursions.
  - If temperature monitoring technology is not implemented properly, nuisance alarms may ensure from several root causes *(e.g., door ajar, power source, probe placement, WIFI connectivity)*.
  - Alternatively, if true, temperature monitoring alarms are not addressed in a timely manner resulting sub-optimal storage conditions may result in drug quality issues.

Safety

- Clinical implications from temperature excursions or unsafe storage practices may include sub-potent products, package contamination, therapeutic failure and patient harm.[5,7-11]
- The ISMP Medication Errors Reporting Program (MERP) received **>100** reports involving neuromuscular blocking agents (NMBAs),[9] e.g., succinylcholine, rocuronium, pancuronium and atracurium.
  - NMBAs are stored in refrigerators in various procedural POC areas.
  - **154** total errors were reported to ISMP MERP over 5 years.
  - Of all wrong-drug errors reported, 50% involved NMBAs *(a subset of error types)*.
  - **80%** of these wrong-drug errors reached the patient, **25%** resulting in patient harm.

Unsafe storage cases[9]

- NMBA was stored in the nursery POC per anesthesiologists' request for access convenience to the adjoining procedural room.
- NMBA was accidentally mistaken for hepatitis B vaccine; **one infant sustained permanent injury** and **another died.**

- Inappropriate vaccine storage has been implicated in numerous reports of vaccine-related adverse events.
  - Additionally University of Utah Drug Information Services (UUDIS)[5] reports from 2001 – 2015 vaccines may represent **2.8%** of all drugs on shortage, but those on the pediatric schedule had a median shortage duration of **21.7** months.
- CDC's Vaccine Adverse Event Reporting System (VAERS), 2008 – 2012 report[10]:
  - There were **476** reports of vaccines kept outside of recommended temperatures, with a median time of **51** hours; local injection reactions represented most adverse events reported (***66%***); two reports implicated multiple patients contracting diseases they were vaccinated against.

Costs

- Vaccine for Children (VFC) audits from DHHS Office of Inspector General report[12]:
  - Mean single-refrigerator inventory **$24,054** *(range **$563 – $110,275**)*
  - **3%** of vaccines found to be expired in an audit, totaled waste of **$14,645** *(sample 45 sites)*; if extrapolated to all VFC doses nationally, cost total **$2.4M**
- Equipment failure
  - A VA hospital in California lost **$60,000**[13] worth of medication due to an overnight refrigerator failure
    - Non-medical grade refrigerators used to store herpes zoster vaccines (***$100 per dose***) in outpatient clinics; 'losses were significant' noted Melissa A. Chase, PharmD, Chief of Pharmacy Services
- Diversion of expensive refrigerated medication[11]
  - Single diversion event example **$12K**
  - 3-year diversion example **$14M**

Temperature monitoring case study

"Collaboration among departments, proper planning, and effective communication were essential elements of the project. Ultimately, the implementation of system-wide, automated temperature monitoring ensures that every refrigerated medication in the Cone Health system is adequately monitored, thus guaranteeing medication viability at the time of administration."[14]

James Mundy, PharmD; Robert P. Granko, PharmD, MBA; Michael Hayes, PharmD, MBA
Cone Health Network, North Carolina *(including 100 locations, 6 hospitals, 1254 acute care beds)*

Diversion case story[11]

Refrigerated medication **diversion case story** how $14M vanished from a University of Miami Hospital

- Pharmacy Technician **Manuel Gerardo Pacheco** charged with four counts of grand theft, two counts of trafficking in contraband prescription drugs and one count of dealing in stolen property
  - Audit found discrepancies on **680 units** of **Neulasta®** *(pegfilgrastim)* between purchase and dispensing *(December 2010 and April 2011)*
  - UM investigator monitoring cameras caught Pacheco removing medications from refrigerators and placing them in his pocket, totaling **$12,416**
  - Search of Pacheco's home found **163 doses** of **Neulasta®** and **20 doses** of **Aloxi®** *(palonosertron)*; investigators also found doses of **Avastin®** *(bevacizumab)*, **Rituxan®** *(rituximab)*, **Aranesp®** *(darbepoetin alfa)*, **Velcade®** *(bortezomib)* and oxaliplatin; totaling **$734,639**
  - The hospital later confirmed Pacheco's diversion over a 3-year period totaled **$14,358,637**
  - Pacheco sentenced to 2 years in prison and required to pay **$9M** as part of plea deal
- Additionally, his type of behavior impacts medication availability with the potential for further patient harm

Conclusions

Refrigerated medication management is complex, and may be further complicated by numerous and disconnected workflows, disparate technologies and storage options. Further research is warranted on the direct economic burden of hospital system-level inefficiencies in refrigerated medication management from the acute and outpatient perspectives, where there is an observed literature gap. Future research on evolving technologies and practice improvements may provide improved visibility and traceability of medications, which can help further optimize refrigerated medication management.

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