ETIOLOGY OF DRUG SHORTAGES

National
- Raw Material Acquisition
- Natural Disaster
- Increased Demand
- Manufacturer Issue

Regional
- Underestimate needs
- Weather
- Fail to order

IMPACT

Clinical
- Delays in drug therapy
- Missed doses
- Alterations in dose or regimen
- Less effective treatment

Financial
- Higher cost drugs
- Violations of contract agreements
- Added resources to manage drug shortages

Safety
- Medication errors
- Adverse drug reactions

IMPACT ON CLINICAL OUTCOMES

Patient Outcomes Caused by Drug Shortages

<table>
<thead>
<tr>
<th>Patient Outcome</th>
<th>Respondent (%)</th>
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</thead>
<tbody>
<tr>
<td>Delay of therapy</td>
<td>75%</td>
</tr>
<tr>
<td>Suboptimal treatment</td>
<td>75%</td>
</tr>
<tr>
<td>Unable to provide recommended drug</td>
<td>71%</td>
</tr>
<tr>
<td>Increased pain or discomfort</td>
<td>5%</td>
</tr>
</tbody>
</table>

ISMP 2017 Survey

Impact of drug shortages on children with cancer — The example of Mechlorethamine

- Mechlorethamine shortage emerged in 2009
- Stanford V regimen amended to include cyclophosphamide 650 mg/m²
- Compared probability of EFS among 181 patient treated with Stanford V to modified Stanford V using cyclophosphamide
- Treatment with cyclophosphamide was significantly less effective (2-year EFS 75%, vs. cyclophosphamide [75, 12.5%] vs. 88% with mechlorethamine [36, 3.5%, P=0.01])
- Relapse necessitated salvage therapy (intensive cytoreduction followed by autologous SCT)
- Added risk of infertility
- Other long-term toxic effects

FINANCIAL IMPACT

Organizational Resources
- Increased personnel costs:
  - Develop plans
  - Bolster inventory
  - Compound drug products
  - Change information systems
  - Time averted from patient care and medication safety

<table>
<thead>
<tr>
<th>Number of FTEs Needed to Sustain Patient Care Caused by Drug Shortages</th>
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</thead>
<tbody>
<tr>
<td>Respondents (N = 366)</td>
</tr>
<tr>
<td>0.5 FTE</td>
</tr>
<tr>
<td>1.5 FTE</td>
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<tr>
<td>2.0 FTE</td>
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<tr>
<td>2.5 FTE</td>
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<tr>
<td>3.0 FTE</td>
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</tbody>
</table>

Number of FTEs Needed to Sustain Patient Care Caused by Drug Shortages
Impact on Medication Safety

Medication errors are more likely to occur when:
1. A different brand or concentration of medication must be purchased
2. Clinicians must order an alternative medication with which they are unfamiliar
   - Look-alike sound-alike
   - Dosing differences
   - Drug propinquity

Other Factors:
- Products provided by compounding pharmacies
- Poor quality compounding resulting in contaminated products
- Imported of equivalent or similar products from other markets
- Counterfeit drugs
- Contamination
- No active ingredient
- Wrong active ingredient

Impact on Medication Safety

ISMP 2017 survey on impact of drug shortages
- 21% of respondents were aware of the occurrence of at least one medication error
- 47% associated with the incorrect dose or concentration

Examples:
- Hydromorphone prescribed as morphine, resulted in death of two patients
- Use of phenytoin injection to manage a fosphenytoin shortage resulted in anaphylaxis and cardiac arrest due to the incorrect infusion rate
- Cytarabine dosing error occurred when a pharmacist used a mixing protocol for 500 mg vials (50 mg/ml) but was actually using a 1,000 mg vial
- Methotrexate dosing error occurred when a pharmacist used a mixing protocol for 500 mg vials (50 mg/ml, not available) but was actually using a 1,000 mg vial
- Physician prescribed the wrong dose of levoleucovorin, the patient received less than the intended dose

Impact on Medication Safety

Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012
- Requires manufacturers to notify FDA of any disruptions or discontinuations which might lead to a shortage of prescription drugs for serious illnesses 6 months in advance or as practicable thereafter but not later than 5 business days after interruption in manufacturing
- Enables FDA to work with manufacturers to increase production, allow for expedited review of another company’s abbreviated NDA, or begin the process of controlled importation of drug to meet demand

ISMP 2017 survey: few respondents reported consistent notifications from manufacturers, wholesalers/distributers, or FDA about drug shortages (12%), their cause (13%), or duration (11%). Improved from 2010 survey in which 84% of respondents said they never or rarely received advanced notifications.

MITIGATION

On July 2018, FDA Commissioner Scott Gottlieb, MD announced the formation of a new Drug Shortages Task Force
- Expand the work of a group created by FDASIA and gives new authorities to address shortages
- To produce drugs with robust manufacturing processes
- To encourage stronger ties to ensure expansion of manufacturing capacity and enhanced quality
- To determine if a critical drugs list should be developed which would deem these as a priority to sustain for the protection of public health
- To explore manufacturing issues with steps to produce new technologies that can improve manufacturing (already implemented as emerging technology program)
**MITIGATION**

**Institutional**
- Develop interdisciplinary committees involved in oversight and management of supply issues
- Determine policy on how drug shortages are managed
- Gray market
- 503B outsourcing facilities

**Operational Assessment**
- Obtain shortage details
- Determine stock on hand
- Determine supply from predetermined alternative sources
- Evaluate purchase history
- Estimate time to impact on care
- Assess supply of alternative products

**Therapeutic Assessment**
- Determine patient population affected and identify alternative treatment options

**Impact Analysis**
- Therapeutic differences, prescribing process, distribution process, administration process
- Establish plan
- Timeline and assign tasks
- Communicate
- Shortage, Effective date, Therapeutic alternative, Temporary guideline, Temporary procedure
- Implement
- Information system, technological, Inventory system, procedure

**IMPACT ON DANA-FARBER CANCER INSTITUTE (DFCI)**

- Pharmacy & Therapeutics Committee responsible for hospital medication use policies, procedures, practices and safety
- Medical Staff Executive Committee
- A Medication Supply Task Force was created by the Pharmacy & Therapeutics Committee to oversee the proactive management of actual and potential drug shortages
- A Drug Product Review Committee developed to evaluate new drug products and minimize impacts on medication safety.

**MEDICATION SUPPLY TASK FORCE**

**Objectives:**
- Monitoring of commercially available drug supply
- Identify alternative agents or regimens in case of supply interruption
- Develop processes and triggers to alert clinicians of potential supply issues based on usage patterns and drug availability
- Establish process for drug allocation, dose adjustments, ordering changes, preparation changes, etc
- Oversight of potential medication safety issues that could result from supply interruptions such as changes in standard drug concentrations, dosage, administration guideline changes
- Communication of drug shortage information

**DRUG PRODUCT REVIEW COMMITTEE**

**Committee Members:**
- Product purchaser
- Materials management
- IV room supervisor
- Regulatory & Compliance Manager
- Information systems CBA
- Clinical Pharmacy Manager
- Medication Safety Officer

**Objectives:**
- Mitigate the risk of medication errors by reviewing all new medications that enter the institute
- Ensure that all information systems are updated to allow medication safety tools to function appropriately
- Proactively assess drug products for medication safety issues and identify and implement solutions to mitigate problems

**EXAMPLE: PRODUCT REVIEW**

**Tasks:**
- Review every new NDC that will be used
- Evaluate plan for use:
  - Location
  - Storage
  - Packaging
  - Ordering
  - Preparation
  - Administration
  - DHR medication list changes
  - Technologic system
  - Inventory system
  - Staff communication/education
- Assess inventory supply and days on hand
### Inventory Review of Currently Backordered Product

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Location</th>
<th>3 month usage</th>
<th>QOH</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Zoster Vaccine</td>
<td>- recombinant, adjuvanted (Shingrix)</td>
<td>Londonderry Central Pharmacy</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Milford Central Pharmacy</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y5 Central Pharmacy</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>Ceftriaxone 1gm vials + bags</td>
<td>Londonderry Central Pharmacy</td>
<td>D</td>
<td>D</td>
<td>D</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Pedi Pharmacy</td>
<td>F</td>
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<tr>
<td></td>
<td></td>
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<td>Ceftriaxone 500mg vials</td>
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<td></td>
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<td>Zoledronic Acid 4mg/5ml</td>
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<td>South Shore Central Pharmacy</td>
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<td></td>
<td>St. Elizabeth Central Pharmacy</td>
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<td></td>
<td></td>
<td>Y5 Central Pharmacy</td>
<td>P</td>
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<td>Doxorubicin liposomal 20mg</td>
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**CASE EXAMPLES**

**DEXRAZOXANE**

**Indication**
- Extravasation
- Cardioprotection

**Packaging**
- 500 mg lyophilized powder
- 250 mg vial

**Preparation**
- Reconstitute with 50 mL of 0.167 Molar sodium lactate injection
- Reconstitute with 25 mL Sterile Water for Injection
- Reconstitute with 50 ml of 0.167 Molar sodium lactate injection

**Vial concentration**
- 10 mg/ml
- 20 mg/ml

**Final IV bag for administration concentration**
- 1000 ml 0.9% Sodium Chloride Lactated Ringer's Injection (1.3-5 mg/mL)
- Lactated Ringer's Injection (4-10 mg/ml) **Note:**
- 0.9% Sodium Chloride 5% Dextrose 1.3-5 mg/ml

**Expiration (RT)**
- 4 hours
- Immediate use
- 6 hours

**Administration**
- Infusion over 1-2 hours
- IV Push or rapid infusion

**DEXRAZOXANE: COMMUNICATION**

**BENDAMUSTINE**

- Management of Information Technology Systems
  - March 2016
  - New medication build (ERX) and validation
  - New medication administration template with chemotherapy treatment plan
  - Pending kit change administration time in system for patients with treatment plans already applied
    - Feb 2018
    - Add medication administration instructions to chemotherapy treatment plan
    - Remove administration instructions from chemotherapy treatment plans
    - Change medication list and time changes with inventory status
    - Sept 2018
    - Automation for Pharmacy
    - Communication
**Impact on cancer patients**

- **Oncology Patients**
  - Palliative Care Pharmacist provided a daily review of all patient profiles and opioid needs.
  - Converted patients to oral opioid medications as appropriate.
  - Maintained continuity of non-opioid use.
  - Localized formulary restrictions on the use of IV analgesics.
  - Assessed potential use of adjuvant ketamine or IV lidocaine for patients with severe pain and high opioid consumption.
  - Centralized the inventory of IV opioids.

**IV INFUSIONS**

- **Therapeutic substitution**
  - Converted patients to non-opioid medications.
  - Products with differing safety profiles with which there is unfamiliarity.

**PN 201**

- **Parenteral Nutrition**
  - Formulation and distribution of PN solutions.
  - Preparation of PN solutions for patients with severe fluid and electrolyte imbalances.

**ORAL OPIOIDS**

- **General fluid replacement needs**
  - Assisted in formulating PN solutions for patients with severe fluid and electrolyte imbalances.

**DIAGNOSTIC INJECTIONS**

- **Injection sites**
  - Injection concentrations.
  - Administration of injections.

** IMMUNE GLOBULIN (GAMMAGARD) & AMINO ACIDS**

- **Therapeutic substitution**
  - Provided a daily review of all patient profiles and opioid needs.
  - Converted patients to oral opioid medications as appropriate.

**COMPOUNDING SODIUM CHLORIDE SOLUTIONS**

- **Preparation**
  - Compounding sodium chloride solutions from sterile water for injection and concentrated sodium chloride.
  - Utilizing large volume minibags (50 ml) to large volumes, to 8% sodium chloride, “keep vein open” and to flush lines.

**CONCLUSIONS**

- Stakeholders and the FDA continue to work on identifying potential solutions.
- Mitigate the effects by developing an infrastructure for dealing with shortages before they occur.
- Success is found with effective information-gathering, treatment to assess impacts and options, ability to function, and implement a plan; coordination of changes in information systems, and a mandate from staff involved in the medication use process.

**ASHP Injectable Opioid Shortage FAQ**

- Supply is unavailable.
- No alternative brand/generic available.
- Unknown when supply will return to market.
- Responding to patients who received their first dose, will complete their treatment.
- Delaying treatment for new patients.
- Appropriate candidates may receive Zoster Vaccine Live (Zostavax®).
RESOURCES

ASHP
- Drug shortage database
- Small-Volume Parenteral Solutions Shortages Suggestions for Management and Conservation
- Injectable Opiod Shortage FAQ
- ASHP Guidelines on managing drug product shortages

FDA
- Drug shortages database
- Report on Drug Shortages for Calendar Year 2017

University of Utah Drug Information Service

ISMP Newsletters

QUESTIONS?