“We’re Out of What?” – Navigating Drug Shortages

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We will be discussing off-label medication use.

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OBJECTIVES

• Define trends of current drug shortage

• Identify causes of drug shortages

• Describe impact of drug shortages on patient safety/cost of healthcare

• Propose strategies to manage shortages

• Interpret restriction guidelines for backordered medications
There's a drug shortage. I'm thinking of replacing your meds with eight hugs a day before & after meals!
BACKORDERS AND THE PRESS

PBS  The New York Times
THE WALL STREET JOURNAL
The Washington Post  ajc
CBS NEWS  Los Angeles Times
USA TODAY  chron
Chicago Tribune

DEPARTMENT NAME

Texas Children’s
PUBLICATIONS BY THE AMERICAN JOURNAL OF HEALTH SYSTEM PHARMACY

- 08/01/01: ASHP Guidelines on Managing Drug Product Shortages
- 11/15/02: Provisional observations on drug product shortages: Effects, causes, and potential solutions
- 10/01/04: National Survey of the impact of drug shortages in acute care hospitals
- 08/01/09: ASHP Guidelines on Managing Drug Product Shortage in Hospitals and Health Systems
- 07/01/11: Impact of drug shortages on US health systems
National Drug Shortages

Annual New Shortages by Year

January 2001 to December 31, 2014

01 02 03 04 05 06 07 08 09 10 11 12 13 14

120 88 73 58 74 70 129 149 166 211 267 204 140 185
National Drug Shortages

Active Shortages by Quarter
January 1, 2010 to December 31, 2015

Source: University of Utah Drug Information Service 2016
National Drug Shortages
Common Drug Classes in Short Supply
New Shortages Reported: 2010-2014

![Bar chart showing the number of drug shortages in various classes from 2010 to 2014.](chart.png)
National Drug Shortages

Reasons for Shortages * - 2014

- Unknown: 47%
- Manufacturing Problems: 25%
- Supply / Demand: 17%
- Raw Material Problems: 2%
- Business decision / Discontinued: 9%
CAUSES

- Limited raw or bulk material
- Regulatory issues
- Voluntary recalls
- Change in product formulation
- Change in manufacturer
- Business decisions
- Moving production locations
- Inventory management strategies
- Acute changes in usage patterns
- Alternative sources of medications
- Natural disasters
CLINICAL IMPACT OF DRUG SHORTAGES

• Failure to treat or progression of disease
• Higher drug acquisition costs
• Increased personal costs
• Lack of adherence to clinical trial protocols
• Loss of trust between healthcare professionals
• Safety issues
  • Compromise of safety measures
  • Medication errors and patient harm
OTHER EFFECTS OF DRUG SHORTAGES

• Financial effects
  • High cost associated with alternative medications
  • Additional costs associated with treatment of adverse outcomes
  • Time and resources spent to address shortages

• Emotional effects
  • Frustration, anger, mistrust
  • Strained professional relationships
COST OF DRUG SHORTAGES (JAN-DEC 2010)

- Infectious Disease
- Surgery
- Oncology
- Cardiovascular
- Neurology
- Endocrinology
- Pain Management
- Psychiatry
- Allergy
- Gastrointestinal
- Emergency Care
FDA’S APPROACH DURING SHORTAGE

• Address manufacturing /quality problems

• Encourage other manufacturer’s to “ramp up”

• Expedite issues related to shortages

• Temporary importation
LIMITATION OF FDA’S AUTHORITY

• Inability to force a manufacturer to produce a product

“Manufacturers are not required to report plans to discontinue a product unless they are the sole manufacturer of a drug that is life-supporting; life-sustaining; or intended for use in the prevention of a debilitating disease or condition...”

(21 CFR 314.81 FR published 10/07)

• No penalty for not notifying FDA of a discontinuation
Manufacturers’ requirement:

- Notify the FDA of any manufacturing “discontinuance, interruption, or other adjustment” that would “likely” result in a shortage of the product.

- Incur fine for not notifying the government about a likely shortage.
“PRESERVING ACCESS TO LIFE-SAVING MEDICATIONS ACT” (S.296)

- FDA requirement:
  - Use evidence-based criteria to identify drugs that may be vulnerable to a shortage
  - Collaborate with manufacturers for “continuity of operations plans” for “medically necessary drugs” and include in those plans a process for addressing drug shortages
“PRESERVING ACCESS TO LIFE-SAVING MEDICATIONS ACT” (S.296)

- FDA requirement:
  - *Put a priority on inspecting facilities that manufacture, propagate, compound, or process a drug involved in a drug shortage and that also have recently corrected a problem*
  - *Distribute, “to the maximum extent practicable,” information on actual drug shortages to health care provider and patient organizations*
IMPACT ON PEDIATRICS

• Pediatric drugs most affected
• No available alternative for specific drugs/concentration
• Higher risk of errors with product changes (concentrations, repackaging, etc.)
• Inability to predict utilization due to seasonality/patient type/size difference
• Increased emotional impact
GUIDELINES FOR MANAGING DRUG SHORTAGES

• Assessment of duration of shortage
• Analysis of threat to patient care and cost
• Exploration of therapeutic alternatives
• Effective/Timely communication
• Patient prioritization
• Ensure external relationships
STEPS TAKEN BY PHARMACY DEPARTMENT

**ASHP GUIDELINE**

- Validate details of shortage
- Identify primary patient population
- Determine:
  - stock on hand
  - supply from alternative sources
  - purchase history and/or true history
- Identify alternative drug product supply

**PHARMACY**

- Effective collaboration to develop tactics around a specific drug/patient population
- Change concentrations or package size
- Compound and repackage drugs/Minimize waste
- Centralize drug supply
- Ensure routine/updated communication
- Engage area hospitals to share supply
- Work with vendors and distributors
WHAT NEEDS TO BE DONE?

• Clinical
  • Work with stakeholders
    • Identify appropriate alternative
    • Create criteria for use/restrictions
  • Update order sets or protocols
  • Send memo to medical staff/ancillary staff

• Operational
  • Add alternative agent to database
  • Create scanning labels to order
  • Set up charges for billing
  • Create dilution labels/add to reconstitution chart
TCH EXPERIENCE

• Communication
  • Appropriate timing
  • Target audience
  • Method of communication

• Ethical dilemma
  • Patient prioritization

• System Limitation
  • Complexity of the system

• Increased costs
TCH EXPERIENCE

• Compromise of safety measures
  • Look-A-Like drugs
  • Standard concentrations
  • Preparation of products

• Increased workload
  • Compounding and repackaging
  • Finding drug supply
  • Establishing guidelines or identifying alternatives
USE OF ALTERNATIVE AGENTS

• Morphine
  • Hydromorphone dosed as morphine resulting in death of two patients and the over sedation of one who required naloxone
  • Wrong dose of hydromorphone administered

• Heparin
  • Wrong dose and frequency of enoxaparin prescribed

• Fosphenytoin
  • Rapid infusion of phenytoin leading to severe thrombophlebitis in a pediatric patient and arrhythmia and cardiac arrest in an surgical patient
USE OF ALTERNATIVE AGENTS

• Chemotherapy
  • Vincristine dosing error occurred when substituted for vincristine
  • Wrong dose of levoleucovorin when used instead of leucovorin
  • Capecitabine use instead of leucovorin resulted in serious GI toxicity in many patients

• Sulfamethoxazole and Trimethoprim
  • Refractory cases of PCP resulted from alternative treatment with clindamycin and primaquine

• General Concerns
  • Mass conversion back and forth can cause problems
CHANGE CONCENTRATION/PACKAGE SIZE/DOSAGE FORM

- Neuromuscular Blocking Agents
  - Wrong dose of succinylcholine administered when different concentration used

- Morphine
  - Administered 4mg believing vial held 2 mg
  - Administered 8 mg instead of 2 mg because only 8 mg syringes available from manufacturer
  - Administered 10 mg of morphine instead of 1 mg due to change in concentration stocked (10 mg/mL instead of 1 mg/mL)
  - 10 mg vials filled in 2 mg vial spot in cabinet
  - 4 mg/mL prefilled syringes replaced with 5 mg/mL vials and wrong dose administered (bar coding system had been overridden due to backorder so it was not caught)
CHANGE CONCENTRATION/PACKAGE SIZE/DOSAGE FORM

• Epinephrine
  • 1:10,000 epi on backorder – 1:1,000 replaced it in code carts: nurse didn’t dilute and patient died of 10 fold overdose during code
  • Pre-filled syringes replaced with ones with intra-cardiac needles and during code, nurse stuck needle into tubing, necessitating change in tubing during the code

• Heparin
  • Vials containing wrong strength heparin stocked in dispensing cabinet
  • Vial of new concentration of heparin looked similar to magnesium and was administered instead of magnesium during a code
CHANGE CONCENTRATION/PACKAGE SIZE/DOSAGE FORM

• Chemotherapy
  • Cytarabine dosing error occurred because dilution instructions for 500 mg vial used when alternative vial of 1000 mg was being used
  • Vial of dry powder was being used to replace pre-diluted methotrexate - was reconstituted incorrectly and patient received wrong dose

• Others
  • Ondansetron vials which looked like hydralazine vials ordered to replace backordered prefilled syringes - stocked in hydralazine bin and sent to patient unit
WORSENED OUTCOMES

- No Therapy/Delayed Therapy
  - Inability to treat PCP due to no IV sulfamethoxazole and trimethoprim
  - Clinically significant delay in treating a patient with PCP due to IV sulfamethoxazole and trimethoprim shortage: patient had to be transferred to receive it
  - Death from resistant pseudomonas infection due to amikacin shortage
  - Readmission of a patient with resistance to amikacin alternatives
  - Patient required helicopter transfer to another hospital for IV acyclovir treatment, causing increase in length of hospitalization
  - Chemotherapy treatments delayed
  - Chemoembolization delayed due to unavailability of mitomycin
  - Deterioration after receiving partial dose imiglucerase d/t backorder
  - Delays in treatment of hypoglycemia when alternatives to D50 vials couldn’t be located in unit
DRUG SHORTAGE SURVEY - IMPACT

- Medication safety issue or error
- Delay or cancellation of a patient care intervention
- Increase in costs
FOOD AND DRUG ADMINISTRATION (FDA) APPROACH DURING SHORTAGE

• Address manufacturing /quality problems

• Encourage other manufacturers to “ramp up”

• Expedite issues related to shortages

• Temporary importation
July 9, 2012: Legislation was passed that gave the FDA new authority to combat drug shortages as well as impose new requirements on manufacturers.

The Food and Drug Administration Safety and Innovation Act (FDASIA) established an “early notification requirement” for manufacturers of drugs that are life-supporting, life-sustaining, or treat a debilitating disease when it discontinues a product or experiences a production interruption.
PROGRESS HAS BEEN MADE

**Shortages Reported**
- 2011: 251
- 2012: 183
- 2013: 117
- 2014: 84
- 2015: 44

**Shortages Averted**
- 2011: 191
- 2012: 165
- 2013: 213
- 2014: 170
- 2015: 145

**All Forms**
- 2011: 101
- 2012: 62
- 2013: 142
- 2014: 92
SHORTAGES IN SHORT

• **Problems**
  - Difficult to impossible to predict
  - Little to no information from manufacturers
  - Increased cost and emotions
  - No evidence of relief from shortages

• **Solutions**
  - Work together as a multidisciplinary team to create guidelines for use, when possible
  - Use cost-saving and resource-sparing measures when appropriate
• National awareness and advocacy about all drug shortages is crucial
  • Pediatrics is bearing the brunt of this – oncology, anesthesiology and others - we have fewer meds, fewer options when shortages exist
  • Presidential action increased awareness, but not clear if it has changed supplies
• Ultimate solution must be via government action
  • No simple solution - pending legislation would mandate better notification, but not more production
• International supplies should be evaluated urgently and long-term by FDA
• Much better communication and sharing of info and resources is needed at all levels
EXAMPLES OF DRUG SHORTAGE MANAGEMENT
SHORTAGE SCENARIO

• You are in the Emergency Department and a patient is admitted with appendicitis. You know at your institution about 20% of patients with appendicitis have *Pseudomonas*. You try to order piperacillin/tazobactam per your normal institutional guidelines, but you find that it is currently on shortage? What do you do?
PIPERACILLIN/TAZOBACTAM (ZOSYN®)

• Beta-lactam/beta-lactamase inhibitor antibiotic with broad coverage
  • Gram-positive, Gram-negative, anaerobes
• Uses:
  • Used for coverage of *P. aeruginosa*, other hospital-associated organisms
  • TCH sepsis algorithm
  • TCH febrile neutropenia algorithm
  • TCH appendicitis/appendectomy guideline
PIPERACILLIN/TAZOBACTAM (ZOSYN®)

- Who must absolutely get it?
  - Most patients can receive another agent
    - Need to prevent overuse of meropenem
- Do we have the alternative agents we need?
  - Formulary: ceftazidime, meropenem, fluoroquinolones
  - Non-formulary: cefepime
**PIPERACILLIN/TAZOBACTAM (ZOSYN®)**

- Emergency addition of cefepime to formulary
- Revision of TCH guidelines

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<tr>
<th>TCH Guideline</th>
<th>Alternate Antimicrobial</th>
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| FEVER AND NEUTROPENIA                  | • Low risk – cefTAZidime  
• High risk – cefepime¹  
• High risk with GI issues/typhlitis – cefepime + metronidazole  
NOTE: High-risk patients should have vancomycin added, as per existing guidelines. |
| ACUTE APPENDICITIS/APPENDECTOMY        | • CefTAZidime + metronidazole                                                          |
| MANAGEMENT GUIDELINE                   |                                                                                       |
| SEPTIC SHOCK - IMMUNOCOMPROMISED HOST  | • Cefepime (+/- metronidazole if intra-abdominal process)                                |
PIPERACILLIN/TAZOBACTAM (ZOSYN®)

• Further steps
  • Monitoring use of cefepime
  • Targeted guidance by clinical pharmacists, infectious disease team, and antimicrobial stewardship committee
SEDATION SHORTAGE

• Starting in 2011 shortages of intravenous fentanyl, midazolam, lorazepam, and diazepam were reported

• Uses:
  • Operating room / anesthesia
  • Intensive care unit sedation
  • Procedural sedation
  • Pain management
  • Seizures / status epilepticus
  • Spasticity
SEDATION SHORTAGE

• Who must absolutely get these agents?
  • Many patients absolutely need sedation and pain management
  • Other agents can be considered for many patients
SEDATION SHORTAGE

• Do we have the alternative agents we need?
  • Opioids: hydromorphone, morphine
    • Concerns: hemodynamic stability in cardiac patients, morphine allergic patients
  • Benzodiazepines
    • Sedation
      • Enteral lorazepam
      • Dexmedetomidine
      • Propofol
      • Ketamine
      • Pentobarbital
    • Seizures and spasticity – other routes and medications
SEDATION SHORTAGE

• Recommendations
  • Spasticity: reserve diazepam for strict NPO
  • Sedation:
    • Midazolam should be reserved for:
      • CV post-op patients
      • Patients requiring neuromuscular blockade (NMB) who cannot receive propofol
      • Intractable seizures
    • Reserve fentanyl for:
      • Post-op CV patients
      • Hemodynamically unstable patients
      • Transplant patients
SEDATION SHORTAGE

• Further steps
  • Extensive provider education
    • In-person education
    • Dosing guide
  • Clinical pharmacist presence and recommendations on rounds
HEMATOLOGY/ONCOLOGY IMPACT

- Cancer is the second leading cause of death in children

- Children with cancer represent a very small percentage of all patients with cancer

- Cooperative group trials have produced substantial improvements in survival with the use of specific chemotherapeutic agents
CHEMOTHERAPY FOR CHILDHOOD CANCER

- Products with overall small market share
- Generic products with lower profitability to manufacturers
- Few alternative regimens to the standard of care
- Competition with larger adult cancer centers for product availability
CHEMO BACKORDER MANAGEMENT

• Multidisciplinary approach involving the following components:
  • Creation of guidelines for use
  • Coordination of patient schedules
  • Conservation of available vials based on anticipated doses
  • Anticipation of newly diagnosed patients based on prior usage patterns
  • Knowledge of currently used protocols locally as well as nationally and internationally
ARE THERE BENEFITS TO SHORTAGES?

- Rarely, drug shortages provide opportunities to identify standard practices which may lack evidence or may be outdated or risky to patients and lead to improved patient care
  - Intravenous vitamin K and anaphylaxis risk
  - Choral hydrate
  - Cefepime addition to formulary
  - Decrease overuse of piperacillin/tazobactam
CONCLUSION

- Drug shortages are ubiquitous in health care and are not going away any time soon
- Causes of drug shortages are multi-factorial
- Drug shortages can cause patient harm and increase the cost of health care
- A multidisciplinary, team-based approach is required in identifying alternative therapies and restricting agents when no alternatives are available
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