Research Synthesis: Shortages

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Introduction

The problem of medicines shortages has received increasing attention in recent years, and affects health systems at local, national and global levels. This review identifies and characterizes the literature on medicines shortages, including the definition, causes, consequences and proposals to address shortages, concluding with research gaps.

Search terms

Pharmaceutical/medicine/drug and shortage

Synthesis of the literature

The literature on shortages is considerable,* mainly focused on the description of medicines shortages, its consequences and coping strategies. Publications on the subject are recent, with the great majority having been published after 2011; a large number of these are notes, letters to the editor, comments, opinion articles, and communications.

The majority of papers are concentrated in the United States (US) and in high-income countries. Only 6 studies were found conducted in low and middle-income countries: two from Iran ((Butler, 2013; Gholami, Kamalinia, Ahmadian Attari, & Salamzadeh, 2012), one from Zambia (Chomba et al., 2010), Kenya (Kangwana et al., 2009), Malawi (Lufesi, Andrew, & Aursnes, 2007) and Brazil (Reis & Perini, 2008).

Most articles discussed medicines shortages in general. Of those that examined a specific medicine or therapeutic class, many focused on antineoplastics and immunomodulant agents, followed by parenteral nutrition and its components, and anesthetics. It is worth noting a large number of citations related to oncology medicines for the pediatric population and injectables in general.

Concepts and Definitions
There is no single definition of a shortage. Of the identified articles that include a conceptual discussion, one was an opinion piece (Duffy, 2012) and two were empirical research (De Weerdt, Simoens, Casteels, & Huys, 2015; Reis & Perini, 2008). De Weerdt et al (2015) through a review of the scientific and gray literature and interviews, sought to define the concept of "drug shortage" in the European community. In order to do so, bibliographic searches were carried out in two databases as well as a manual search on the websites of regulatory bodies and professional organizations. The authors also investigated how long a product has to be out of stock to be considered a shortage. They concluded that there were two general definitions of shortages, one referring to when to notify regulatory agencies and another for the designation of a shortage.

There is no unified definition linking these two aspects of shortages, nor to facilitate comparison between different information systems and studies.

Description of the problem

Of the publications that focused on describing shortages, half were composed of communications, editorials, and opinion articles, which in general communicated the existence of shortages, called for action to solve the problem, and/or proposed therapeutic alternatives to medicines in shortage (Alspach, 2012a, 2012b; Carter, 2011; Dal Moro, 2013; Fox & Tyler, 2013; Mayer, 2012; Mirtallo, 2011; Navarro, Norman, Pérez-Molina, & López-Vélez, 2012; Printz, 2012; Tomlin, 2016; Traynor, 2011; Wenzel, 2015). The other papers emphasized the seriousness of the problem, demonstrating that it is a growing problem in recent years, is a part of the daily life of health professionals, reports cases in healthcare settings, and their impact on patients' health (Bauters et al., 2015; Costelloe, Guinane, Nugent, Halley, & Parsons, 2015; Gundlapalli, Beekmann, Graham, & Polgreen, 2013; Hawley, Mazer-Amirshahi, Zocchi, Fox, & Pines, 2016; Hvisdas, Lordan, Pizzi, & Thoma, 2013; Kaposy, 2014; Palm & Dotson, 2015; Pauwels, Huys, Casteels, & Simoens, 2014; Quadri et al., 2015; Reed et al., 2016).

Causes

Only a few studies examined the causes of shortages. Of the three articles identified that did so, two (Lufesi et al., 2007; Woodcock & Wosinska, 2012) were empirical studies while one was an editorial that emphasized the importance of further research on causes (Blum, 2014). From the empirical studies, Lufesi et al (2007) identified as the cause of medicines shortage in Malawi the deficiency of the local distribution system. Woodcock and Wosinka (2012), when analyzing the shortage of injectables in the United States, indicated as causes problems related to the quality of medicines that led to the interruption of production. The authors pointed out that the production of injectables is more complex and expensive, and quality cannot easily be measured by the final consumer. Thus, producers underinvest in infrastructure, eventually leading to problems in manufacturing that may result in shortages. This problem is worsened by the small number of producers of injectables medicines. The authors proposed that regulatory agencies assign quality indicators to production sites to inform consumer decision-making, that financial incentives for higher quality injectable production be provided, and these measures would result in fewer problems with interruption of manufacturing and greater availability (Woodcock & Wosinska, 2012).

Consequences

A number of papers focused on the consequences of shortages. Reported consequences included: substitution for less effective and more toxic therapies for patients (Becker et al., 2013; Kehl et al., 2015; Kosarek, Hart, Schultz, & DiGiovanni, 2011), higher costs (Bible, Evans, Payne, & Mostafavifar, 2014; Dorsey et al., 2009; Havrilesky, Garfield, Barnett, & Cohn, 2012; Hayes, Ward, Slabaugh, & Xu, 2014; M. McLaughlin et al., 2013; Ralls et al., 2012), worsening of biochemical parameters (Corrigan & Kirby, 2012; Davis, Javid, & Horslen, 2014; Pramyothin, Kim, Young, Wichansawakun, & Apovian, 2013), delay in clinical trials (Salazar, Bernhardt, Li, Aplenc, & Adamson, 2015), increased rates of adverse events (Hall et al., 2013; Holcombe, 2012; M. McLaughlin et al., 2013; Sheth, Verrico, Skledar, & Towers, 2005; Wuerz, Bow, & Seftel, 2013), and worse clinical outcomes due to discontinuation of therapy (Ruktanonchai et al., 2014). In contrast, eight papers found no significant differences, or even observed better clinical outcomes of patients after therapy discontinuation or dose reduction (Deroma et al., 2012; Goldblatt, Fletcher, McGill, Szer, & Wilson, 2011; Hughes, Goswami, & Morris, 2015; Storey et al., 2016; Thoma et al., 2014;

Tolia, Murthy, McKinley, Bennett, & Clark, 2014). Interestingly, Liang and Mackey (2012) found that medicines in short supply were being sold online at exorbitant prices, supporting the argument that shortages may fuel underground markets in medicines.

Proposals or Recommendations

In terms of recommendations, publications focused on coping strategies put in place and their results, reported on expert opinions on how to manage medicines shortages, health professionals' perceptions regarding what needed to be done, and/or advocated for certain actions (Barlas, 2013; Eggertson, 2011; Sirrs, 2011; Vogel, 2012). The main coping strategies cited were: fiscal and quality incentives (e.g. letter grades on the quality of manufacturing sites) to companies in exchange for continued production and alteration of the inspection system (Schweitzer, 2013); timely information on shortages for prescribers, patients and pharmacies (Hsia et al., 2015; Mirtallo, Holcombe, Kochevar, & Guenter, 2012); guarantee of an emergency stock of critical drugs (Peter, 2006); preparation of an action plan for cases of shortages, listing priorities for care, management strategies and possible therapeutic alternatives (Beck, Smith, Gordon, & Garrett, 2015; DeCamp, Joffe, Fernandez, Faden, & Unguru, 2014; Krisl, Fortier, & Taber, 2013; Plogsted, Adams, Allen, Breen, et al., 2016; Plogsted, Adams, Allen, Cober, et al., 2016; Singleton et al., 2013; Valgus, Singer, Berry, & Rathmell, 2013); use of therapeutic alternatives, even if they are off-label (Berthe-Aucejo et al., 2014; M. L. de Lemos, Waignein, & Haan, 2016); establishing a partnership with the pharmaceutical industry (Jensen & Throckmorton, 2015); contracting pharmacists specifically to monitor stocks and handle shortages (Caulder, Mehta, Bookstaver, Sims, & Stevenson, 2015); training of health professionals (Eggertson, 2011; Jagsi et al., 2014); use of medicines beyond their expiry date in critical situations (M. de Lemos, Kletas, Man, & Walisser, 2012); use of information systems to monitor adverse effects due to shortages (M. M. McLaughlin, Skoglund, Pentoney, & Scheetz, 2014); and use of alternative infusion techniques to reduce the necessary dose (McHugh & Ibinson, 2013; Parbhoo et al., 2014).

Research gaps

- Conceptual work is needed to better define shortages, stock-outs and when these should be notified to regulatory agencies;
- Further studies on shortages in middle and low-income countries are needed.
- Mapping of active pharmaceutical ingredient (API) and finished product manufacturing sources is needed, especially for off-patent and low-price medicines for which profit margins and the incentive to produce may be relatively low.
- Further research is needed on the causes of medicines shortages, especially analysis that includes global determinants.
- Increased analysis is needed on the range, effectiveness and consequences of coping strategies in the face of shortages.

Notes

[1] This synthesis of the literature is based on a longer review: Chaves LA, Chaves GC, Vianna MNS, Oliveira MA. Desabastecimento de medicamentos na literatura científica da saúde: uma revisão narrativa. Physis Rev Saúde Coletiva. in-press. http://dx.doi.org/10.1590/S0103-73312019290107 (in Portuguese).

Cited papers with abstracts

Alspach, J. G. (2012a). Is the Drug Shortage Affecting Patient Care in Your Critical Care Unit? Critical Care Nurse, 32(1), 8–13. https://doi.org/10.4037/ccn2012810

No abstract available.

Link: https://doi.org/10.4037/ccn2012810

Alspach, J. G. (2012b). The Drug Shortage What Critical Care Nurse Readers Report. Critical Care Nurse, 32(5), 11–13. https://doi.org/10.4037/ccn2012818

No abstract available.

Link: https://doi.org/10.4037/ccn2012818

Barlas, S. (2013). FDA Strategies to Prevent and Respond to Drug Shortages. Pharmacy and Therapeutics, 38(5), 261–263.

Abstract: To stave off a shortage of doxorubicin in 2011 and 2012, the FDA expedited the approval of a company's unapproved manufacturing process. Paying companies sufficiently so that they can invest in their facilities when needed is just one of many steps that could be taken to rectify future shortages.

Bauters, T., Claus, B. O., Norga, K., Huys, I., Simoens, S., & Laureys, G. (2015). Chemotherapy drug shortages in paediatric oncology: A 14-year single-centre experience in Belgium. Journal of Oncology Pharmacy Practice, 1078155215610915. https://doi.org/10.1177/1078155215610915

Abstract: Shortages of chemotherapy are a growing challenge for the healthcare system. We present the burden of drug shortages of chemotherapeutics in the paediatric hemato-oncology unit of a tertiary care hospital and solutions that were used to manage them. Between January 2001 and December 2014, 54 individual shortages were detected, affecting a total number of 21 different drugs. In total, 4127 shortage days were registered with a mean duration of 196.5 SD ± 144.0 days per individual drug shortage. Methotrexate, doxorubicin and carboplatin had the longest supply disruptions. Solutions to address the problems were purchase of a generic alternative, a change of individual treatment plans, cohorting of patients and import from abroad.

Link: https://doi.org/10.1177/1078155215610915

Beck, J. C., Smith, L. D., Gordon, B. G., & Garrett, J. R. (2015). An ethical framework for responding to drug shortages in pediatric oncology: Ethical Framework for Drug Shortages. Pediatric Blood & Cancer, 62(6), 931–934. https://doi.org/10.1002/pbc.25461

Abstract: The frequency of drug shortages has increased considerably over the last decade. Important ethical issues arise whenever the supply of an effective drug is insufficient to meet demand. Using the ethical principles of beneficence, non-maleficence, and justice, institutions

can guide prioritization of drug distribution before a shortage occurs to avoid unfair and unethical distribution of resources. This analysis will give a historical context for drug shortages, identify, and explore the central ethical concerns raised by drug shortages, and propose an ethical framework for addressing them in the context of pediatric oncology.

Becker, D. J., Talwar, S., Levy, B. P., Thorn, M., Roitman, J., Blum, R. H., … Grossbard, M. L. (2013). Impact of Oncology Drug Shortages on Patient Therapy: Unplanned Treatment Changes. Journal of Oncology Practice, 9(4), e122–e128. https://doi.org/10.1200/JOP.2012.000799

Abstract: Drug shortages have substantial economic costs and mandate treatment changes that may affect efficacy and toxicity

Berthe-Aucejo, A., Prot-Labarthe, S., Pull, L., Lorrot, M., Touratier, S., Trout, H., … Bourrat, E. (2014). Traitement de la gale et rupture d'Ascabiol® : quid de la population pédiatrique ? Gale chez l'enfant et rupture d'Ascabiol®. Archives de Pédiatrie, 21(6), 670–675. https://doi.org/10.1016/j.arcped.2014.03.001

Abstract: Scabies is a disease in steady increase in Iˆle-de-France region. Standard treatment, Ascabiol® (benzyl benzoate/sulfiram), is back-order for several months and its return remains uncertain. Facing this drug shortage, French Drug Agency (ANSM) has imported a drug from Germany, Antiscabiosum 10 % (benzyl benzoate), to treat patients having contraindications for other scabicides available in France (ivermectin, esdepallethrine). However, infants less than 1 year (< 15 kg) and asthmatics infants have no alternative treatment. A multidisciplinary workgroup explored the various existing therapeutic alternatives in France and worldwide. From ANSM's recommendations and group's experience, a decision algorithm was proposed for treating patients. However, pediatric context implied the use of off-label drugs. Proposed treatments widely known by practitioners, prescriptions-types, dose, modalities of use and dispensation, and flyers to patients were realized to optimize treatment efficacy.

Bible, J. R., Evans, D. C., Payne, B., & Mostafavifar, L. (2014). Impact of Drug Shortages on Patients Receiving Parenteral Nutrition After Laparotomy. Journal of Parenteral and Enteral Nutrition, 38(2 suppl), 65S-71S. https://doi.org/10.1177/0148607114550317

Abstract: Background: Drug shortages, including parenteral nutrition (PN) product shortages, continue to increase and have a significant impact on healthcare. The extent to which product shortages affect bowel recovery and outcomes in patients receiving PN is unknown. The objective of this study is to examine the impact of extensive PN product shortages on patients receiving PN after laparotomy for bowel obstruction. Methods: A retrospective review was conducted for patients who underwent a laparotomy for small bowel obstruction and received PN postoperatively. Periods of limited and extensive PN product shortages at our institution were defined. PN therapy duration and composition, daily laboratory values, electrolyte supplementation, length of stay, and cost of hospitalization were recorded. Analyses using $\chi 2$, Wilcoxon rank sum, log-rank, and t tests as appropriate were performed using SAS/STAT 9.2. Results: Patients had longer hospital length of stays (20.0 vs 15.2 days; P =.04), trends toward longer PN therapy courses (8.8 vs 6.6 days; P = .13), and a 51% higher hospital cost during the extensive PN drug shortage period. Mean serum electrolyte concentrations were similar while the need for supplemental magnesium replacements increased during the extensive shortage

period (75% vs 35%; P = .01). Supplemented patients also required higher doses of magnesium (2.7 vs 1.0 g; P < .01) and more laboratory draws during the extensive shortage period (59% vs 21% required ≥2 draws daily; P = .04). Fewer lipid calories were delivered during the extensive shortage period (2.4 vs 4.8 kcal/kg/d; P < .01). Conclusion: PN drug shortages have a negative impact on patient outcomes and require aggressive management strategies.

Blum, F. C. (2014). "Doctor, We Have No Saline Today": The Curious Case of the Generic Injectable Drug Shortage. Academic Emergency Medicine, 21(6), 699–700. https://doi.org/10.1111/acem.12398

No abstract available.

Butler, D. (2013). Iran hit by drug shortage. Nature, 504(7478), 15–16. https://doi.org/10.1038/504015a

No abstract available.

Carter, D. (2011). Drug Shortage Crisis Affects Patients and Nurses: AJN, American Journal of Nursing, 111(11), 14. https://doi.org/10.1097/01.NAJ.0000407289.24878.32

No abstract available.

Caulder, C. R., Mehta, B., Bookstaver, P. B., Sims, L. D., & Stevenson, B. (2015). Impact of Drug Shortages on Health System Pharmacies in the Southeastern United States. Hospital Pharmacy, 50(4), 279–286. https://doi.org/10.1310/hpj5004-279

Abstract: Background: Drug shortages have become all too common and affect all aspects of the health care delivery system. The increased number of drug shortages has had a negative impact on patient care as well as costly financial implications. Objectives: This article identifies the current problems and negative outcomes drug shortages have caused and provides a framework for how to best prepare for and combat future shortages. It highlights specific problems faced by health care system pharmacies in the Southeastern United States and the managerial responses to address these shortage situations. Methods: A 34-question, multiple-choice survey was distributed to pharmacy directors in North Carolina, South Carolina, Georgia, and Florida. Results: Of 549 surveys distributed, 219 (40%) responses were received. Respondents reported that drug shortages cause 1% to 5% error rates in hospitals and that 60% of the time drug shortages create unsafe conditions for patients and staff. Many of the respondents reported a 300% to 500% markup on medications on the shortage list. Seventy-six percent of institutions have autosubstitutions for drug shortages that have been preapproved by Pharmacy & Therapeutics Committees. Conclusions: The causes of drug shortages are multifaceted, and the safety and financial implications can be costly. In the short term, health care institutions can utilize pharmacists to assist in circumventing the drug shortage problem. The combined efforts of all health care professionals, the US government, manufacturers, and the lay public are necessary to bring awareness and plausible solutions to the drug shortage problems in the long term.

Chomba, E. N., Haworth, A., Mbewe, E., Atadzhanov, M., Ndubani, P., Kansembe, H., & Birbeck, G.

L. (2010). The Current Availability of Antiepileptic Drugs in Zambia: Implications for the ILAE/WHO "Out of the Shadows" Campaign. The American Journal of Tropical Medicine and Hygiene, 83(3), 571–574. https://doi.org/10.4269/ajtmh.2010.10-0100

Abstract: Recent concerns regarding antiepileptic drug (AED) availability in Zambia led us to conduct a study in the Lusaka and Southern Provinces to quantify the availability and cost of AEDs and assess determinants. Among 111 pharmacies, almost one-half did not carry AEDs (N = 54; 49.1%). Available AEDs were phenobarbitone (21; 18.9%), carbamazepine (27; 24.3%), valproic acid (4; 3.6%), and phenytoin (3; 2.7%). Adult out-of-pocket monthly costs ranged from US $7 to $30. Pediatric syrups were universally unavailable. Interviews revealed several barriers to AED provision, including that handling phenobarbitone (historically the most affordable AED) has become increasingly difficult because of newly enforced regulatory requirements. Personal communications with epilepsy-care providers in other low income countries suggest that this problem may be widespread. Improved enforcement of existing drug regulations may be contributing to the AED shortage. Social programs aimed at encouraging people with epilepsy to come "out of the shadows" must be preceded by improved AED access.

Corrigan, M., & Kirby, D. F. (2012). Impact of a National Shortage of Sterile Ethanol on a Home Parenteral Nutrition Practice A Case Series. Journal of Parenteral and Enteral Nutrition, 36(4), 476– 480. https://doi.org/10.1177/0148607111428453

Abstract: Catheter-related bloodstream infection (CRBSI) is a common and life-threatening infectious complication of home parenteral nutrition (PN). CRBSI is associated with hospital admissions, morbidity, mortality, loss of venous access, and healthcare costs. Ethanol has bactericidal and fungicidal properties, making it an ideal locking solution for preventing CRBSI. The authors report 6 patients with a recurrence of CRBSI when ethanol lock (ETL) was withheld due to a national shortage. This is the first known report of the ramifications of a national ethanol shortage on redevelopment of CRBSI in home PN patients with a history of CRBSIs. This series further supports the existing literature showing that ETL is a viable therapy for the prevention of CRBSIs, warranting prospective research. The impact of an ethanol shortage due to a sole-source manufacturer supports the need for the Food and Drug Administration to regulate pharmaceutical products to avoid shortages.

Costelloe, E. M., Guinane, M., Nugent, F., Halley, O., & Parsons, C. (2015). An audit of drug shortages in a community pharmacy practice. Irish Journal of Medical Science (1971 -), 184(2), 435– 440. https://doi.org/10.1007/s11845-014-1139-7

Abstract: Background There are no firm data on drug shortages in Irish community pharmacy. This prospective observational study aimed to characterise the drug shortage problem in an Irish community pharmacy. Aims The primary aim was to determine numbers and durations of drug shortages. Secondary aims included comparing these shortages with Irish Pharmacy Union (IPU) drug shortage lists and determining the frequency with which notifications were received prior to shortages. Further secondary aims were to examine relationships between causes of drug shortages and drug costs and between causes of drug shortages and shortage durations. Methods The study took place in a community pharmacy in a Limerick City suburb between October 2012 and February 2013. Data were collected daily regarding drugs that were dispensed, but unavailable to purchase. Suppliers/manufacturers provided data on the reasons for shortages. Results 65/1,232 dispensed drugs (5.3 %) were in short supply over the study period.

Median shortage duration was 13 days (interquartile range 4–32 days) and median cost was €8.10. Numbers of unavailable drugs by month varied from 13 to 38. Monthly IPU drug shortage lists identified between six and eight of these shortages depending on the month. Two notifications were received from suppliers/manufacturers regarding shortages. Parallel exports had the highest mean costs (mean €38.05) and manufacturing problems were associated with the longest durations (mean 57.44 days). Conclusions This study highlights the drug shortage problem in an Irish community pharmacy. We propose that enhanced communication between all stakeholders is the most worthwhile solution. Further studies are needed.

Dal Moro, F. (2013). BCG shortage in Europe. Preventive Medicine, 57(2), 146. https://doi.org/10.1016/j.ypmed.2013.04.019

No abstract available.

Davis, C., Javid, P. J., & Horslen, S. (2014). Selenium Deficiency in Pediatric Patients With Intestinal Failure as a Consequence of Drug Shortage. Journal of Parenteral and Enteral Nutrition, 38(1), 115– 118. https://doi.org/10.1177/0148607113486005

Abstract: Background: Parenteral nutrition (PN) is a lifesaving therapy for children with intestinal failure and can now be used chronically without the life-threatening complications of the past. Adequate intravenous trace element supplementation is required as part of a complete nutrition prescription. According to the U.S. Food and Drug Administration (FDA), the number of drug shortages, including sterile injectable agents used as PN components, has increased since 2010. Selenious acid as an individual additive was recently unavailable at our institution for 9 months due to a national shortage. Materials and Methods: To assess the impact of the selenious acid shortage, we retrospectively compiled data from existing clinical records for eligible patients. We included children with intestinal failure on full PN support who were older than 1 year at the onset of the selenium shortage. Whole-blood selenium concentrations prior to the selenious acid shortage were compared with concentrations drawn during the shortage. Results: Five patients with intestinal failure and complete PN dependence were identified, and all 5 patients had normal serum selenium concentrations prior to the shortage. All 5 patients developed severe biochemical selenium deficiency in direct correlation with the shortage of selenium. No morbidity associated with selenium deficiency was observed. Selenium concentrations recovered after selenium supplementation was reinstituted. Conclusion: A national selenious acid shortage was associated with biochemical selenium deficiency in a cohort of children with intestinal failure. Despite very low selenium concentrations, none of our patients exhibited clinical signs of deficiency.

De Weerdt, E., Simoens, S., Casteels, M., & Huys, I. (2015). Toward a European definition for a drug shortage: a qualitative study. Frontiers in Pharmacology, 6. https://doi.org/10.3389/fphar.2015.00253

Abstract: Background: Drug shortages are currently on the rise. In-depth investigation of the problem is necessary, however, a variety of definitions for 'drug shortages' are formulated in legislations, by different organizations, authorities, and other initiatives. For international comparison, the underlying definition for drug shortages is important to allow appropriate interpretation of national databases and the results of scientific studies. The objective is to identify the different elements which should be considered in a uniform definition for drug

shortages in the European Union (EU) and to detect the different conditions for reporting drug shortages. Materials and Methods: Definitions of drug shortages were searched in the scientific databases as well as in the gray literature. Similar topics were identified and organizations were contacted to formulate the reasoning underlying the definitions. Results: Over 20 different definitions for drug shortages were identified. A distinction is made between general definitions of drug shortages and definitions used for the reporting of drug shortages.

Differences and similarities are observed in the elements within the definitions, e.g., when does a supply problem become a drug shortage, permanent and/or temporally shortages, the typology and time frame of a drug shortage. The moment a supply problem is considered as a shortage, can be defined at four levels: (i) demand side, (ii) supply side, (iii) delivery of a drug, and (iv) availability of a drug. Permanent discontinuations of drugs are not always covered in definitions for drug shortages. Some definitions only consider those drugs used for the treatment of serious diseases or drugs for which no alternative is available. Different time frames were observed, varying between 1 day and 20 days. Conclusion: Obtaining a uniform definition for drug shortages is important as well as identifying which conditions are preferable to report drug shortages in order to facilitate international benchmarking. This paper can be used as a guidance to point out all the different elements which should be considered to formulate a uniform definition to be applied in the EU.

DeCamp, M., Joffe, S., Fernandez, C. V., Faden, R. R., & Unguru, Y. (2014). Chemotherapy Drug Shortages in Pediatric Oncology: A Consensus Statement. Pediatrics, 133(3), e716–e724. https://doi.org/10.1542/peds.2013-2946

Abstract: Shortages of essential drugs, including critical chemotherapy drugs, have become commonplace. Drug shortages cost significant time and financial resources, lead to adverse patient outcomes, delay clinical trials, and pose significant ethical challenges. Pediatric oncology is particularly susceptible to drug shortages, presenting an opportunity to examine these ethical issues and provide recommendations for preventing and alleviating shortages. We convened the Working Group on Chemotherapy Drug Shortages in Pediatric Oncology (WG) and developed consensus on the core ethical values and practical actions necessary for a coordinated response to the problem of shortages by institutions, agencies, and other stakeholders. The interdisciplinary and multiinstitutional WG included practicing pediatric hematologist-oncologists, nurses, hospital pharmacists, bioethicists, experts in emergency management and public policy, legal scholars, patient/family advocates, and leaders of relevant professional societies and organizations. The WG endorsed 2 core ethical values: maximizing the potential benefits of effective drugs and ensuring equitable access. From these, we developed 6 recommendations: (1) supporting national polices to prevent shortages, (2) optimizing use of drug supplies, (3) giving equal priority to evidence-based uses of drugs whether they occur within or outside clinical trials, (4) developing an improved clearinghouse for sharing drug shortage information, (5) exploring the sharing of drug supplies among institutions, and (6) developing proactive stakeholder engagement strategies to facilitate prevention and management of shortages. Each recommendation includes an ethical rationale, action items, and barriers that must be overcome. Implemented together, they provide a blueprint for effective and ethical management of drug shortages in pediatric oncology and beyond.

Deroma, L., Sechi, A., Dardis, A., Macor, D., Liva, G., Ciana, G., & Bembi, B. (2012). Did the temporary shortage in supply of imiglucerase have clinical consequences? Retrospective observational

ABOUT US

The Knowledge Network on Innovation and Access to Medicines is a project of the Global Health Centre at the Graduate Institute, Geneva. The project seeks to maximize the contributions of research and analysis to producing public health needs-driven innovation and globally-equitable access to medicines.

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study on 34 italian Gaucher type I patients. JIMD Reports, 7, 117–122. https://doi.org/10.1007/8904_2012_158

Abstract: Background. Enzyme Replacement Therapy (ERT) is the standard of care in Gaucher disease. The effects of withdrawal or reduced doses are debated, thus a retrospective cohort study was conducted to investigate clinical and laboratory differences in 34 Gaucher type 1 patients experiencing an ERT dosage reduction after the forced temporary imiglucerase shortage in 2009. Methods. Haemoglobin concentration, leukocytes and platelets counts, and chitotriosidase activity were assessed at baseline and after 6 and 12 months (t0, t6, t12), while bone pain, energy, work or school performance, concentration, memory and social life every 3 months. Results. The cohort was made up of 18 males and 16 females (medians: age 41.8 years, therapy duration 14.1 years, dosage reduction 35.5%). Haemoglobin, leukocytes and platelets remained substantially stable, while chitotriosidase activity showed an increase, especially after t6. Age, splenectomy or genotype were not associated with laboratory parameters changes, except for a significant median increase of chitotriosidase activity in non-splenectomised patients after 12 months (p = 0.01). At 3, 6, 9 and 12 months, more than 50% patients reported at least one problem in subjective well-being (56%, 65%, 70%, 58%, respectively), while bone pain occurred or worsened in 13/33, 13/32, 7/28 and 5/26 patients, respectively. No bone crises were reported. Conclusions. Drug reduction did not induce substantial modification in the laboratory values but seems to have influenced the well-being perception of some Gaucher patients. Thus, bone pain, general health and quality of life should be carefully monitored during ERT reductions.

Dorsey, E. R., Thompson, J. P., Dayoub, E. J., George, B., Saubermann, L. A., & Holloway, R. G. (2009). Selegiline shortage. Neurology, 73(3), 213–217. https://doi.org/10.1212/WNL.0b013e3181ae7b04

Abstract: Background: In September 2007, shortages of generic selegiline occurred, forcing patients to either switch to more expensive alternatives or forego treatment. We sought to evaluate prescription trends of generic selegiline and to quantify the economic impact of any resulting drug substitution of more expensive alternatives. Methods: We analyzed proprietary data from IMS Health on monthly prescriptions in the United States for selegiline and potential substitutes from February 2002 through December 2007. Linear regression was used to predict the number of expected prescriptions after August 2007 had a shortage not occurred. The main outcome measures were the changes in prescriptions filled and the economic impact of drug substitution. Results: Prior to the shortage, total prescriptions filled for generic selegiline decreased 42%, and supply consolidated into one company, Apotex Inc., Toronto, Canada, whose market share increased from 41% to 83%. During the first 4 months of the shortage, Apotex Inc. filled 10,500 fewer prescriptions than projected and other selegiline manufacturers filled 7,400 more than projected for a net shortage of 3,100 prescriptions. The number of branded selegiline capsules filled during this period increased by 1,800 above projections, and 1,300 prescriptions for generic selegiline were not refilled or substituted. The societal cost of substituting generic selegiline with branded capsules was $75,000 over the first 4 months of the shortage. Conclusions: Generic drug shortages carry economic and health implications. Given ongoing consolidation in the generics drug industry, these shortages may become more common and may require heightened regulatory scrutiny of the generic drug industry.

Duffy, E. (2012). Drug Shortage Crisis Resolution. Journal of Pharmacy Practice, 25(6), 619–620. https://doi.org/10.1177/0897190012460987

No abstract available.

Eggertson, L. (2011). Drug shortage registry under discussion. CMAJ : Canadian Medical Association Journal, 183(10), E637–E638. https://doi.org/10.1503/cmaj.109-3904

No abstract available.

Fox, E. R., & Tyler, L. S. (2013). Call to Action: Finding Solutions for the Drug Shortage Crisis in the United States. Clinical Pharmacology & Therapeutics, 93(2), 145–147. https://doi.org/10.1038/clpt.2012.225

Abstract: In their article in this issue of CPT, Woodcock and Wosinska are the first to clearly outline the quality and manufacturing problems causing drug shortages of generic injectables. These authors have focused on the main issue, namely, that manufacturing problems and the lack of incentives for quality products are the primary reasons for most recent shortages of generic injectable drugs

Gholami, K., Kamalinia, G., Ahmadian Attari, M. M., & Salamzadeh, J. (2012). Three Years Evaluation of Drug Shortages from Educational Pharmacies in Tehran. Iranian Journal of Pharmaceutical Research : IJPR, 11(2), 565–572.

Abstract: The effectiveness of any drug supply systems in providing a trustworthy supply of essential drugs is a critical issue. To evaluate this effectiveness, it is necessary to watch over the status of the essential medicines in any country impartially and continuously. Some countries and also the World Health Organization (WHO) have codified a list of minimum medicines needed for a basic health care system and published them in assortments as a list of essential medicines. The aim of this study was to give an evaluation of the shortages status in Iran and identify the strengths and weaknesses of policies made in Ministry of Health during the years 2005 to 2008 in providing the essential drugs based on the WHO list of essential medicines., The reports used in this retrospective study were collected from the central purchasing unit of one of the main chain drugstores in the country (13-Aban Pharmacy) every 2 to 3 weeks. In these reports, a drug is added to the list of shortages when the requested drug is not delivered. The reports were studied and the results were analyzed based on the WHO list of essential medicines and the national drug list of Iran. The shortages always included 20 to 40 medicines from the list of essential drugs compiled by WHO. Based on this finding, the Ministry of Health and particularly Food and Drug Organization can compile a National List of Essential Medicines and try to always supply them and prevent their shortage.

Goldblatt, J., Fletcher, J. M., McGill, J., Szer, J., & Wilson, M. (2011). Enzyme replacement therapy "drug holiday": Results from an unexpected shortage of an orphan drug supply in Australia. Blood Cells, Molecules, and Diseases, 46(1), 107–110. https://doi.org/10.1016/j.bcmd.2010.05.002

Abstract: The development of recombinantly manufactured enzyme replacement therapy (ERT) has revolutionised the management of some inherited disorders of metabolism. Gaucher

disease was the first lysosomal storage disorder for which ERT became commercially available and ERT remains first- line treatment for affected individuals. In Australia, 70 patients with Gaucher disease are treated through a centrally administered Australian Government national program known as the Life Savings Drug Program (LSDP). Imiglucerase (Cerezyme®), manufactured by Genzyme Corporation, is the only ERT currently registered in Australia for the treatment of Gaucher disease. In June 2009, Genzyme Corporation announced the detection of a virus in its Allston Landing manufacturing facility which resulted in inventories of imiglucerase being insufficient to meet projected global demand. The Australian Government sought advice from its Gaucher Disease Advisory Committee (GDAC) on recalculating patient doses in order to ration available imiglucerase to those most in need on a clinical severity basis. Management of this rationing process was urgent and required extensive investigation to develop a clinical severity hierarchy, to review available imiglucerase stock spread across multiple pharmacies, to implement a strategy for redistributing available imiglucerase according to specific patients' recalculated doses, to advise treating doctors and patients concerning these changed circumstances and to consider new monitoring schedules during the drug shortage phase. A cohort of 24 patients was withdrawn from therapy, 22 of whom had no discernable clinical adverse effect. This experience suggests that short-term studies of maintenance therapy without a no-treatment arm may lead to erroneous conclusions and that some patients may have treatment holidays or delayed infusions without short-term adverse outcomes.

Gundlapalli, A. V., Beekmann, S. E., Graham, D. R., & Polgreen, P. M. (2013). Perspectives and concerns regarding antimicrobial agent shortages among infectious disease specialists. Diagnostic Microbiology and Infectious Disease, 75(3), 256–259. https://doi.org/10.1016/j.diagmicrobio.2012.11.020

Abstract: Antimicrobial shortages have made treating certain infections more difficult. A web-based survey asking about experience with antimicrobial drug shortages was distributed in 2011 to 1328 infectious diseases physician members of the Emerging Infectious Diseases Network of the Infectious Diseases Society of America. A majority (78%) of 627 respondents reported needing to modify antimicrobial choices because of drug shortages within the past 2 years. Antimicrobials most often reported as not available or available but in short supply were trimethoprim–sulfamethoxazole injection (by 65% of respondents), amikacin (by 58%), aztreonam (by 31%), and foscarnet (by 22%). Most respondents (55%) reporting a shortage indicated that the shortage adversely affected patient outcomes and that they were forced to use alternative and second line agents which were either less effective, more toxic, or more costly. Most (70%) indicated that they learned about the shortage from contact with the pharmacy after trying to prescribe a drug in short supply. More effective means of informing physicians about drug shortages is critical to lessen the impact on patient care.

Hall, R., Bryson, G. L., Flowerdew, G., Neilipovitz, D., Grabowski-Comeau, A., & Turgeon, A. F. (2013). Drug shortages in Canadian anesthesia: a national survey. Canadian Journal of Anesthesia/Journal Canadien d'anesthésie, 60(6), 539–551. https://doi.org/10.1007/s12630-013-9920-z

Abstract: Background: Canadian physicians are faced with an increasing frequency of drug shortages. We hypothesized that drug shortages have a clinical impact on anesthesia care in Canada. Methods: We conducted a self-administered survey of anesthesiologists in Canada using the membership list of the Canadian Anesthesiologists' Society. For survey development,

we identified key domains, including types of drug shortages, impact on the ability of anesthesia practitioners to provide general anesthesia care, and impact on patient outcomes. We undertook assessments of face validity, clinical sensibility, and content validity. Respondents were surveyed from January-April 2012. Results: Completed valid questionnaires were submitted by 1,187 respondents (61.4%), and 779 (65.7%) of respondents described a shortage of one or more anesthesia or critical care drugs. Changes in anesthesia practice resulting from drug shortages were common; 586 (49%) respondents thought they had given an inferior anesthetic, and 361 (30%) reported administering medications with which they were unfamiliar. Respondents also reported that drug shortages were, at times, responsible for changes in the conduct of patient care, with 28 (2.4%) noting cancellation or postponement of surgery and 92 (7.8%) witnessing a drug error. One hundred sixty-five (13.9%) respondents regarded drug shortages as having prolonged recovery from anesthesia, and 124 (10.5%) viewed drug shortages as resulting in an increased number of postoperative complications, such as postoperative nausea and vomiting. Interpretation: Drug shortages are common in anesthetic practice in Canada. This state of affairs may have a negative effect on how anesthesiologists practice anesthesia and may be associated with adverse patient outcomes.

Havrilesky, L. J., Garfield, C. F., Barnett, J. C., & Cohn, D. E. (2012). Economic impact of paclitaxel shortage in patients with newly diagnosed ovarian cancer. Gynecologic Oncology, 125(3), 631–634. https://doi.org/10.1016/j.ygyno.2012.03.028

Abstract: Objective: To determine the potential economic impact of a paclitaxel drug shortage in patients with newly diagnosed, untreated ovarian cancer. Methods. A modified Markov state transition model with a 6 cycle time horizon compared two scenarios: (1) Standard treatment (STD): paclitaxel 175 mg/m2/carboplatin AUC 5 ×6 cycles; (2) Paclitaxel drug shortage (DS): docetaxel 75 mg/m2/carboplatin AUC 5 × 6 cycles. Adverse events, quality of life, and costs of chemotherapy, neuropathy, febrile neutropenia, and anemia were incorporated. Key assumptions: (1) Costs and consequences were assigned only to grade 2+ neuropathy, febrile neutropenia, and grade 3–4 anemia; (2) Grade 2+ neuropathy prompted a switch from paclitaxel/carboplatin to docetaxel/carboplatin or from docetaxel/carboplatin to carboplatin alone; (3) Febrile neutropenia resulted in inpatient hospitalization followed by G-CSF prophylaxis. Results: The mean cost of 6 cycles of chemotherapy was $4939 in the STD and $16,107 in the DS scenario, for a cost difference of $11,168 per patient over 6 cycles of treatment. STD was the dominant strategy (less expensive and more effective than the drug shortage scenario). In sensitivity analysis, DS was more costly over a wide range of clinical estimates in each arm. A drug shortage that affects approximately 50% of women initiating chemotherapy is expected to impact 779 women and cost third party payers an additional $8,699,872 monthly. Conclusions: Our model indicates that chemotherapy drug shortages can have a significant negative impact on the average cost of primary treatment for ovarian cancer and have the potential to negatively impact health system costs.

Hawley, K. L., Mazer-Amirshahi, M., Zocchi, M. S., Fox, E. R., & Pines, J. M. (2016). Longitudinal Trends in U.S. Drug Shortages for Medications Used in Emergency Departments (2001-2014). Academic Emergency Medicine, 23(1), 63–69. https://doi.org/10.1111/acem.12838

Abstract: Objectives: This was a study of longitudinal trends in U.S. drug shortages within the scope of emergency medicine (EM) practice from 2001 to 2014. Methods: Drug shortage data from the University of Utah Drug Information Service were analyzed from January 2001 to March

2014. Two board-certified emergency physicians classified drug shortages based on whether they were within the scope of EM practice, whether they are used for lifesaving interventions or high-acuity conditions, and whether a substitute for the drug exists for its routine use in emergency care. Trends in the length of shortages for drugs used in EM practice were described using standard descriptive statistics and regression analyses. Results: Of the 1,798 drug shortages over the approximately 13-year period (159 months), 610 shortages (33.9%) were classified as within the scope of EM practice. Of those, 321 (52.6%) were for drugs used as lifesaving interventions or for high-acuity conditions, and of those, 32 (10.0%) were for drugs with no available substitute. The prevalence of EM drug shortages fell from 2002 to 2007; however, between January 2008 and March 2014, the number of EM drug shortages sharply increased by 435% from 23 to 123. From January 2008 to March 2014 shortages

in drugs used as a direct lifesaving intervention or for high-acuity conditions increased 393% from 14 to 69, and shortages for drugs with no available substitute grew 125% from four to nine. Almost half (46.6%) of all EM drug shortages were caused by unknown reasons (the manufacturer did not cite a specific reason when contacted). Infectious disease drugs were the most common EM drugs on shortage, with 148 drug shortages totaling 2,213 months during the study period. Conclusions: Drug shortages impacting emergency care have grown dramatically since 2008. The majority of shortages are for drugs used for lifesaving interventions or high-acuity conditions. For some, no substitute is available.

Hayes, M. S., Ward, M. A., Slabaugh, S. L., & Xu, Y. (2014). Lessons from the Leucovorin Shortages Between 2009 and 2012 in a Medicare Advantage Population: Where Do We Go from Here? American Health & Drug Benefits, 7(5), 264–270.

Abstract: Background Three distinct shortages of the generic drug leucovorin, a reduced form of folic acid used in several chemotherapy regimens, were reported by the US Food and Drug Administration (FDA) between 2008 and 2014. Levoleucovorin, an alternative therapy to leucovorin, failed to demonstrate superiority over leucovorin in clinical trials and is substantially more expensive. Objective To calculate the impact of the leucovorin shortages on primary treatment costs to patients and a health plan, and to present strategies for health plans to deal with future drug shortages. Methods This retrospective descriptive study was conducted using Humana's Medicare Advantage prescription drug plan administrative claims database between January 1, 2009, and December 31, 2012. A total of 1542 patients with at least 1 medical or pharmacy claim for either leucovorin or levoleucovorin during the first 3 months of the respective plan year (between 2009 and 2012) who had continuous enrollment for the entirety of the same plan year, were included in this study. Trends in primary treatment costs—defined as the drug cost of leucovorin or levoleucovorin—over the 4-year evaluation period were assessed. The mean annual patient out-of-pocket (OOP) costs and the mean plan-paid per member per month (PMPM) costs were also calculated. Results The percentage of patients receiving leucovorin decreased annually, with a 15.8% drop from 2010 to 2011. This reduction was accompanied by a 6.6% increase in patients receiving levoleucovorin. The mean annual patient OOP costs were $167 to $714 higher for levoleucovorin than for leucovorin. Similarly, the mean plan-paid PMPM costs were higher (up to $1667 PMPM) for levoleucovorin than for leucovorin. The aggregate costs for the 2 drugs increased steadily, including the patient OOP costs and the plan-paid PMPM costs. The most prominent cost increase occurred between 2010 and 2011, with a 3.8-fold increase in patient OOP costs and a 5-fold increase in the plan-paid PMPM costs. This corresponded to the timing of the second leucovorin shortage announcement by the FDA in June 2010. Conclusions Health plans can play an important role in minimizing the impact of drug

shortages by identifying the affected patient population, identifying therapeutic alternatives, assisting providers with alternative sourcing strategies when possible, adjusting approval processes, and implementing quality management or pathway programs.

Holcombe, B. (2012). Parenteral Nutrition Product Shortages Impact on Safety. Journal of Parenteral and Enteral Nutrition, 36(2 suppl), 44S-47S. https://doi.org/10.1177/0148607111434777

Abstract: The drug shortage crisis continues in the United States and threatens the integrity of the pharmaceutical supply chain and compromises patient care, especially patients requiring parenteral nutrition (PN) therapy. The number of new drug shortages has increased rapidly over the past 5 years, with the most significant increase in sterile injectable products. The most common reason for a shortage of a sterile injectable medication is a product quality issue. Two surveys of healthcare professionals have assessed the impact of drug shortages on patient safety. Participants in one survey reported over 1000 medication errors or patient adverse events as the result of shortages. The American Society for Parenteral and Enteral Nutrition also conducted a survey of healthcare professionals regarding PN product shortages and the associated patient care implications. Safety risks were reported throughout the entire PN process, from procurement of PN products to patient outcomes. Providing PN therapy during product shortages requires vigilance and continuous assessment of the entire PN process to optimize patient care quality and avoid patient harm.

Hsia, I. K.-H., Dexter, F., Logvinov, I., Tankosic, N., Ramakrishna, H., & Brull, S. J. (2015). Survey of the National Drug Shortage Effect on Anesthesia and Patient Safety: A Patient Perspective. Anesthesia & Analgesia, 121(2), 502–506. https://doi.org/10.1213/ANE.0000000000000798

Abstract: BACKGROUND: There are few data on patients' desire to be informed of drug shortages before elective surgery. We surveyed patients who had previously undergone laparoscopic cholecystectomy for their opinions. METHODS: Nine hundred forty-nine Mayo Clinic patients were invited to participate in the survey. The postal survey posed a hypothetical surgical scenario and requested answers regarding the desire to be informed and to postpone scheduled surgery because of neostigmine shortage. Comparison was made with Canadian patients from a hospital in Ontario. RESULTS: Most of the 256 respondents wanted "to be told by the anesthesia doctor about the neostigmine shortage" if there were "slight differences" in side effects between the drug combinations (P < 0.0001). The percentage of patients wanting to know was 76.2% (95% confidence interval, 70.5%–81.3%). Secondary analyses tested the validity and reliability of the survey. With each increase in the differences in substituted drug's side effects, there was a progressive increase in the patients' desire for information (P < 0.0001; 73.2%, 76.2%, and 95.7% of 246, 256, and 253 respondents, respectively) and preference for delaying surgery (P < 0.0001; 33.6%, 39.4%, and 80.9% of 238, 246, and 241 respondents, respectively). There was no association with respondents' sex (P = 0.19), age (P = 0.76), educational level (P = 0.39), or country (United States versus Canada [n = 58]; P = 0.87). CONCLUSIONS: The majority (>50%) of surveyed patients want to be informed of drug shortages that might affect their care.

Hughes, K. M., Goswami, E. S., & Morris, J. L. (2015). Impact of a Drug Shortage on Medication Errors and Clinical Outcomes in the Pediatric Intensive Care Unit. The Journal of Pediatric Pharmacology and Therapeutics : JPPT, 20(6), 453–461. https://doi.org/10.5863/1551-6776-20.6.453

Abstract: OBJECTIVES: The purpose of this study was to assess the rate of prescribing errors, resulting adverse events, and patient outcomes associated with sedation and analgesia in the pediatric intensive care unit (PICU) before and during a national shortage of fentanyl and injectable benzodiazepines., METHODS: A retrospective chart review was performed of patients admitted to the PICU with at least 1 prescribed order for a sedative or analgesic agent during the time periods of January to February of 2011 and 2012. Initial orders for sedative and analgesic agents were identified and investigated for appropriateness of dose and were assessed for error-associated adverse events. Orders were stratified by timing in regard to clinical pharmacist on-site availability. Demographic and outcome information, including unintended extubations, ventilator days, and PICU length of stay, were gathered., RESULTS: One hundred sixty-nine orders representing 72 patients and 179 orders representing 75 patients in 2011 and 2012, respectively, were included in analysis. No differences were found in the rate of prescribing errors in 2011 and 2012 (33 errors in 169 orders vs. 39 errors in 179 orders, respectively, p=0.603). No differences were found in rates of prescribing errors in regard to clinical pharmacist on-site availability. A significant increase was seen in unintended extubations per 100 ventilator days, with 0.15 in 2011 vs. 1.13 in 2012, respectively (p<0.001). A significant decrease was seen in ventilator days per patient (p<0.001) and PICU length of stay per patient (p=0.019)., CONCLUSIONS: There were no differences in rates of prescribing errors before versus during the fentanyl and benzodiazepine shortage.

Hvisdas, C., Lordan, A., Pizzi, L. T., & Thoma, B. N. (2013). US Propofol Drug Shortages: A Review of the Problem and Stakeholder Analysis. American Health & Drug Benefits, 6(4), 171–175.

Abstract: Background: Drug shortages have increased in recent years in the United States, with a majority involving sterile injectable drugs. Propofol, a sterile injectable drug, is frequently used as a sedative, thanks to its rapid onset of action and a short recovery period. However, propofol is complicated and expensive to manufacture, and recent events involving major manufacturers have led to shortages of the drug in the United States. Objectives: To review the events leading to the shortage of propofol and to discuss how the shortage is affecting various healthcare stakeholders, as an example of the systemwide problem of drug shortages in the United States. Discussion: Manufacturers currently have little economic incentive to produce propofol, a generic drug whose production is costly and carries a high liability. The enforcement of good manufacturing practices by the US Food and Drug Administration is beneficial for the safety of US citizens, but it can inherently lead to a sudden halt in the manufacturers' production of drugs. Hospitals are affected because they must develop a plan to address current and potential shortages, including restricting the use of medications that have a shortage and shifting to alternative agents. Conclusion: The shortage of propofol significantly impacted the delivery of care in the United States in 2009, and various stakeholders are working to increase the existing supply of propofol and to investigate the use of alternative medications when the supply runs short. The case of propofol presented in this article is used to illustrate a systemwide view of the impact of drug shortages on the US healthcare system.

Jagsi, R., Spence, R., Rathmell, W. K., Bradbury, A., Peppercorn, J., Grubbs, S., & Moy, B. (2014). Ethical Considerations for the Clinical Oncologist in an Era of Oncology Drug Shortages. The Oncologist, 19(2), 186–192. https://doi.org/10.1634/theoncologist.2013-0301

Abstract: The authors review the history, causes, and regulatory context of oncology drug shortages in the U.S., as well as the literature, policy analyses, and other relevant sources to

provide oncologists with ethical guidance when faced with oncology drug shortages. Practical recommendations are discussed., Shortages of injectable drugs affect many cancer patients and providers in the U.S. today. Scholars and policymakers have recently begun to devote increased attention to these issues, but only a few tangible resources exist to guide clinical oncologists in developing strategies for dealing with drug shortages on a recurring basis. This article discusses existing information from the scholarly literature, policy analyses, and other relevant sources and seeks to provide practical ethical guidance to the broad audience of oncology professionals who are increasingly confronted with such cases in their practice. We begin by providing a brief overview of the history, causes, and regulatory context of oncology drug shortages in the U.S., followed by a discussion of ethical frameworks that have been proposed in this setting. We conclude with practical recommendations for ethical professional behavior in these increasingly common and challenging situations.

Jensen, V., & Throckmorton, D. C. (2015). Shortage of Peritoneal Dialysis Solution and the Food and Drug Administration's Response. Clinical Journal of the American Society of Nephrology, 10(8), 1484–1486. https://doi.org/10.2215/CJN.12061214

Abstract: Although the number of new drug shortages has been lower in recent years than in the past, severe shortages have occurred that have affected large numbers of patients. A new law entitled the Food and Drug Administration Safety and Innovation Act was enacted in July of 2012, which requires companies to notify the Food and Drug Administration of anticipated shortages. This notification requirement has allowed the Food and Drug Administration to work closely with manufacturers earlier to mitigate and, often, prevent shortages. However, not all shortages are able to be prevented, and the shortage of peritoneal dialysis solution is one that has had a significant effect on patients. The Food and Drug Administration continues to use all available tools to address this shortage with manufacturers, including temporary availability of imported peritoneal dialysis solution from Ireland. Mitigating shortages is a top priority for the Food and Drug Administration, and communication with all stakeholders is essential.

Kangwana, B. B., Njogu, J., Wasunna, B., Kedenge, S. V., Memusi, D. N., Goodman, C. A., … Snow, R. W. (2009). Malaria Drug Shortages in Kenya: A Major Failure to Provide Access to Effective Treatment. The American Journal of Tropical Medicine and Hygiene, 80(5), 737–738.

Abstract: A key bench mark of successful therapeutic policy implementation, and thus effectiveness, is that the recommended drugs are available at the point of care. Two years after artemether- lumefathrine (AL) was introduced for the management of uncomplicated malaria in Kenya, we carried out a cross-sectional survey to investigate AL availability in government facilities in seven malaria- endemic districts. One of four of the surveyed facilities had none of the four AL weight-specific treatment packs in stock; three of four facilities were out of stock of at least one weight-specific AL pack, leading health workers to prescribe a range of inappropriate alternatives. The shortage was in large part caused by a delayed procurement process. National ministries of health and the international community must address the current shortcomings facing antimalarial drug supply to the public sector.

Kaposy, C. (2014). Drugs, Money, and Power: The Canadian Drug Shortage. Journal of Bioethical Inquiry, 11(1), 85–89. https://doi.org/10.1007/s11673-013-9494-z

ABOUT US

The Knowledge Network on Innovation and Access to Medicines is a project of the Global Health Centre at the Graduate Institute, Geneva. The project seeks to maximize the contributions of research and analysis to producing public health needs-driven innovation and globally-equitable access to medicines.

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Abstract: This article describes the shortage of generic injectable medications in Canada that affected hospitals in 2012. It traces the events leading up to the drug shortage, the causes of the shortage, and the responses by health administrators, pharmacists, and ethicists. The article argues that generic drug shortages are an ethical problem because health care organizations and governments have an obligation to avoid exposing patients to resource scarcity. The article also discusses some options governments could pursue in order to secure the drug supply and thereby fulfill their ethical obligations.

Kehl, K. L., Gray, S. W., Kim, B., Kahn, K. L., Haggstrom, D., Roudier, M., & Keating, N. L. (2015). Oncologists' Experiences With Drug Shortages. Journal of Oncology Practice, 11(2), e154–e162. https://doi.org/10.1200/JOP.2014.000380

Abstract: Most oncologists encountered drug shortages in the year before our survey, but experiences with shortages varied with practice structure. Further research is needed to quantitatively assess the impact of drug shortages on patients.

Kosarek, L., Hart, S. R., Schultz, L., & DiGiovanni, N. (2011). Increase in Venous Complications Associated With Etomidate Use During a Propofol Shortage: An Example of Clinically Important Adverse Effects Related to Drug Substitution. The Ochsner Journal, 11(2), 143–146.

Abstract: Etomidate is a widely used intravenous induction agent that is especially useful for patients at risk for hypotension during anesthesia induction. Side effects limiting its use include adrenocortical suppression, acidosis, myoclonus, venous irritation, and phlebitis. The osmolality of etomidate prepared in propylene glycol appears to play a crucial role in causing phlebitis. The increased use of etomidate during the recent propofol shortage correlated with an increase in reported incidences of postoperative phlebitis and thrombophlebitis at Ochsner Clinic Foundation from October 2009 through April 2010. Several methods aim to prevent such occurrences, including pretreatment with lidocaine (and possibly esmolol), lower doses of etomidate, and injection into larger veins. The most compelling evidence suggests that using a lipid formulation of etomidate instead of the traditional propylene glycol preparation may dramatically decrease venous sequelae.

Krisl, J. C., Fortier, C. R., & Taber, D. J. (2013). Disruptions in the Supply of Medications Used in Transplantation: Implications and Management Strategies for the Transplant Clinician: Critical Drug Shortages in Solid Organ Transplant. American Journal of Transplantation, 13(1), 20–30. https://doi.org/10.1111/j.1600-6143.2012.04308.x

Abstract: Drug shortages are a threat to patient care and public health, and the number of drugs on shortage is growing at an exponential rate. The major therapy areas affected by these shortages are oncology, anti-infective, cardiovascular and central nervous system. However, drugs utilized in the transplant patient population have not been exempt, and can have significant influence on posttransplant outcomes. The purpose of this review is to discuss the current and historical solid organ transplant-related disruptions in the supply of medications and implications on patient care and safety. Transplant centers should be armed with an implementation plan when imperative transplant- related drugs such as tacrolimus, mycophenolate, or antithymocyte globulin go on shortage. This plan should provide steps to manage the shortage, and provide effective therapeutic alternatives.

Lemos, M. de, Kletas, V., Man, S., & Walisser, S. (2012). Using expired supply in times of drug shortage. Journal of Oncology Pharmacy Practice, 18(2), 319–319. https://doi.org/10.1177/1078155212442562

No abstract available.

Lemos, M. L. de, Waignein, S., & Haan, M. de. (2016). Evidence-based practice in times of drug shortage. Journal of Oncology Pharmacy Practice, 22(3), 566–570. https://doi.org/10.1177/1078155215589980

Abstract: Shortage of oncology drugs is a particularly complicated issue because there are usually limited therapeutic options. Moreover, oncology practice may employ medications for supportive indications which differ from their main usage. This means shortage of oncology drugs is not usually addressed by the major drug shortage guidelines. We have previously shown that, during a shortage crisis, it is possible to make a recommendation on the use of an expired drug supply based on a reasonable estimate of its safety and efficacy. Here, we would like to share further examples on how to deduce potential therapeutic alternatives based on pharmacokinetic and pharmacodynamic principles in the absence of direct clinical evidence in the literature.

Liang, B. A., & Mackey, T. K. (2012). Online Availability and Safety of Drugs in Shortage: A Descriptive Study of Internet Vendor Characteristics. Journal of Medical Internet Research, 14(1), e27. https://doi.org/10.2196/jmir.1999

Abstract: BACKGROUND: Unprecedented drug shortages announced by the US Food and Drug Administration (FDA) have severely affected therapeutic access, patient safety, and public health. With continued shortages, patients may seek drugs online. OBJECTIVE: To assess the prevalence of online marketing for current FDA shortage drugs and potential patient safety risks. METHODS: We performed a descriptive study of the prevalence of online marketing for shortage drugs-that is, offers for sale of each drug, including characteristics of online drug sellers and intermediary sites marketing these drugs. RESULTS: Of the 72 FDA shortage-listed drugs, 68 (94%) were offered for sale online. We found 291 offers for these drugs, the vast majority (n = 207, 71.1%) by online drug sellers selling direct to consumers. Intermediary sites included data aggregators (n = 22, 8%), forum links (n = 23, 8%), and personal page data links (n = 34, 12%), as well as Flickr social media links (n = 5, 2%), all advertising drugs without a prescription. Of the 91 online drug sellers identified, 31 (34%) had more than 1 shortage drug offered for sale, representing most (n = 148, 71%) of all online drug seller sales offers. The majority of these online drug sellers (n = 21, 68%) were on the National Association of Boards of Pharmacy (NABP) Not Recommended Sites list. Finally, for shortage drugs with an online drug seller (n = 58, 85%), 53 (91%) had at least one site on the Not Recommended list and 21 (36%) had only sites on the Not Recommended list. CONCLUSIONS: FDA shortage drugs are widely marketed over the Internet. Suspect online drug sellers and intermediaries dominate these sales offers. As a critical risk management issue, patients, providers, and policymakers should be extremely cautious in procuring shortage drugs through Internet sourcing.

Lufesi, N. N., Andrew, M., & Aursnes, I. (2007). Deficient supplies of drugs for life threatening diseases in an African community. BMC Health Services Research, 7, 86. https://doi.org/10.1186/1472-6963-7-86

Abstract: Background In Malawi essential drugs are provided free of charge to patients at all public health facilities in order to ensure equitable access to health care. The country thereby spends about 30% of the national health budget on drugs. In order to investigate the level of drug shortages and eventually find the reasons for the drugs shortages in Malawi, we studied the management of the drug supplies for common and life threatening diseases such as pneumonia and malaria in a random selection of health centres. Methods In July and August 2005 we visited eight out of a total of 37 health centres chosen at random in the Lilongwe District, Malawi. We recorded the logistics of eight essential and widely used drugs which according to the treatment guidelines should be available at all health centres. Five drugs are used regularly to treat pneumonia and three others to treat acute malaria. Out-of-stock situations in the course of one year were recorded retrospectively. We compared the quantity of each drug recorded on the Stock Cards with the actual stock of the drug on the shelves at the time of audit. We reviewed 8,968 Patient Records containing information on type and amount of drugs prescribed during one month. Results On average, drugs for treating pneumonia were out of stock for six months during one year of observation (median value 167 days); anti- malarial drugs were lacking for periods ranging from 42 to138 days. The cross-sectional audit was even more negative, but here too the situation was more positive for anti-malarial drugs. The main reason for the shortage of drugs was insufficient deliveries from the Regional Medical Store. Benzyl penicillin was in shortest supply (4% received). The median value for non-availability was 240 days in the course of a year. The supply was better for anti-malarial drugs, except for quinine injections (9 %). Only 66 % of Stock Card records of quantities received were reflected in Patient Records showing quantities dispensed. Conclusion We conclude that for the eight index drugs the levels of supply are unacceptable. The main reason for the observed shortage of drugs at the health centres was insufficient deliveries from the Regional Medical Store. A difference between the information recorded on the Stock Cards at the health centres and that recorded in the Patient Records may have contributed to the overall poor drug supply situation. In order to ensure equitable access to life saving drugs, logistics in general should be put in order before specific disease management programmes are initiated.

Mayer, D. K. (2012). Anatomy of a Drug Shortage. Clinical Journal of Oncology Nursing, 16(2), 107–108. https://doi.org/10.1188/12.CJON.107-108

No abstract available.

McHugh, S. M., & Ibinson, J. W. (2013). Anesthesiology in the era of drug shortages: use of a succinylcholine infusion for a laparoscopic sigmoid colectomy due to a shortage of neostigmine. Journal of Clinical Anesthesia, 25(1), 79–81. https://doi.org/10.1016/j.jclinane.2012.07.003

No abstract available.

McLaughlin, M., Kotis, D., Thomson, K., Harrison, M., Fennessy, G., Postelnick, M., & Scheetz, M. H. (2013). Effects on patient care caused by drug shortages: A survey. Journal of Managed Care Pharmacy, 19(9), 783–788.

Abstract: BACKGROUND: Drug shortages pose a serious challenge for health care institutions, often interfering with patient care. A common practice during a drug shortage is to select an

alternate therapeutic; however, these agents often present challenges and may create safety concerns. Patient harms including adverse events and medication errors may occur. Patients may also file complaints because of drug shortages. OBJECTIVE: To measure the effect of drug shortages on patient outcomes, clinical pharmacy operations, patient complaints, and institutional cost. METHODS: An e- mail link to an online survey was sent to pharmacy director members in the MedAssets Pharmacy Group Purchasing Organization. Data were collected within a 3-week period from October 2-23, 2012.

The survey focused on 6 different domains: demographics, adverse events, medication errors, patient outcomes, patient complaints, and institutional cost. RESULTS: The survey was sent to 1,516 directors of pharmacy. There were 193 respondents (response rate 13%) who participated in the survey. Approximately 40% of respondents reported between 1 and 5 adverse events probably or possibly associated with drug shortages at their institution. The majority of respondents reported between 1 and 10 medication errors. The most common types of medication errors reported were omission (n=86, 55.5%), wrong dose dispensed/administered (n=85, 54.8%), and wrong drug dispensed/administered (n=54, 34.8%). The most common outcomes reported by respondents were alternative medication used (n=146, 85.3%), delay of therapy (n=121, 70.8%), and increased patient monitoring necessary (n=84, 49.1%). Patient complaints were reported by 38% of respondents. The majority of respondents reported an estimated quarterly institutional cost from shortages of less than $100,000, and approximately one quarter of respondents reported adding at least 1 full-time equivalent to manage drug shortages. The majority of participant comments mentioned the increasing institutional costs attributed to drug shortages. CONCLUSIONS: Medication errors and adverse events continue to occur from drug shortages, often resulting in inadequate patient care, high institutional costs, and patient complaints. Delayed care and cancelled care have been reported from shortages. Further research is necessary to better classify medication errors and adverse events during a drug shortage.

McLaughlin, M. M., Skoglund, E., Pentoney, Z., & Scheetz, M. H. (2014). Developing a Method for Reporting Patient Harm Due to Antimicrobial Shortages. Infectious Diseases and Therapy, 3(2), 349– 355. https://doi.org/10.1007/s40121-014-0040-z

Abstract: Introduction: The number of drug shortages in the United States has increased in recent years. While some literature exists on factors that contribute to antimicrobial shortages, the need remains to accurately gage the level of patient harm incurred as a result of realized antimicrobial shortages. Furthermore, current methods of reporting adverse drug events are known to under-report instances of patient harm. We sought to develop an ongoing and accurate method of reporting patient harm due to antimicrobial shortages, which was convenient, anonymous, and allowed clinicians to estimate the causality due to a shortage. Methods: We distributed a public SurveyMonkey (SurveyMonkey, Palo Alto, CA, USA) link to gather information regarding institution (for de-duplicating purposes), patient age, sex, antimicrobial product on shortage, type of infection requiring treatment or prophylaxis, adverse event, and patient outcome. Results: To date complete data were reported on four patients being treated for infections that included Stenotrophomonas maltophilia bacteremia, Pneumocystis jirovecii pneumonia, neonatal sepsis of unknown etiology, and cytomegalovirus colitis. Antimicrobials that were unavailable to patients included sulfamethoxazole–trimethoprim, gentamicin, and foscarnet. Two adverse events (a delay in treatment and an inability to treat with other antimicrobials due to resistance) were attributed with probable

causality due to a shortage, while the remaining adverse events (death and an inability to tolerate high oral doses) were attributed to have unlikely and possible causalities due to a shortage, respectively. Conclusion: These methods encourage reports of antimicrobial shortage harms.

Mirtallo, J. M. (2011). The Drug Shortage Crisis. Journal of Parenteral and Enteral Nutrition, 35(4), 433–433. https://doi.org/10.1177/0148607111412051

No abstract available.

Mirtallo, J. M., Holcombe, B., Kochevar, M., & Guenter, P. (2012). Parenteral Nutrition Product Shortages The A.S.P.E.N. Strategy. Nutrition in Clinical Practice, 27(3), 385–391. https://doi.org/10.1177/0884533612444538

Abstract: Product (drug) shortages have had a significant impact on the healthcare system, particularly on patients and clinicians. This has been especially true with patients requiring parenteral nutrition (PN). The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) has dealt with PN product shortages in the past on behalf of its members and their patients. However, the shortage severity and duration have made dealing with the PN product shortages in 2010–2012 extremely challenging

Navarro, M., Norman, F. F., Pérez-Molina, J. A., & López-Vélez, R. (2012). Benznidazole Shortage Makes Chagas Disease a Neglected Tropical Disease in Developed Countries: Data from Spain. The American Journal of Tropical Medicine and Hygiene, 87(3), 489–490. https://doi.org/10.4269/ajtmh.2012.12-0080

Abstract: Chagas disease is a neglected tropical disease endemic in Latin America. The first-line treatment option is benznidazole, but stocks are expected to run out in the coming months. Spain would need around 5 million benznidazole tablets. This drug shortage could make Chagas disease a neglected tropical disease also in developed countries.

Palm, E., & Dotson, B. (2015). Copper and Zinc Deficiency in a Patient Receiving Long-Term Parenteral Nutrition During a Shortage of Parenteral Trace Element Products. Journal of Parenteral and Enteral Nutrition, 39(8), 986–989. https://doi.org/10.1177/0148607114549255

Abstract: Drug shortages in the United States, including parenteral nutrition (PN) components, have been common in recent years and can adversely affect patient care. Here we report a case of copper and zinc deficiency in a patient receiving PN during a shortage of parenteral trace element products. The management of the patient's deficiencies, including the use of an imported parenteral multi–trace element product, is described.

Parbhoo, R. K., Wetz, K., Tschampel, M., Pompili, V., Schenko, E., Mavko, L., & Blais, D. (2014). Innovative Approach to Preparing Radial Artery Cocktails in Response to Manufacturer Shortages of Nitroglycerin and Verapamil. Hospital Pharmacy, 49(7), 628–633. https://doi.org/10.1310/hpj4907-628

Abstract: Background: Transradial access has gained popularity over transfemoral access for cardiac catheterization, because of the decreased risk of bleeding, time to ambulation, and length of stay leading to improved patient satisfaction. One disadvantage of the radial artery approach is vasospasm, which can be prevented with the administration of verapamil and nitroglycerin in a pre- and postradial cocktail. Unfortunately, there have been manufacturer shortages for both of these medications. Methods: The utilization of radial artery cocktails and other nitroglycerin compounding practices were evaluated in response to cost containment and waste reduction initiatives and to medication shortages. Results: A modified process for supplying verapamil and nitroglycerin for the transradial approach via separate syringes enabled physicians to have quick access to the medications and to customize the cocktail based on the patient's needs. This process also decreased costs and minimized wastage. The change in practice decreased waste from 44% for preradial cocktail syringes and 66% for postradial cocktail syringes to 8.7%. Discussion: This process for supplying the medications necessary to perform a radial artery catheterization and intracoronary nitroglycerin has allowed for conservation of commercial product supply.

Pauwels, K., Huys, I., Casteels, M., & Simoens, S. (2014). Drug shortages in European countries: a trade-off between market attractiveness and cost containment? BMC Health Services Research, 14(1), 1.

Abstract: Background: Drug shortages are a global problem. While extensively studied in the United States, numbers about drug shortages in European countries are scarce. This study aims to collect and present data about drug shortages in European countries. Methods: A reporting template for the collection of data about drug shortages was designed based on a literature search. Countries offering a reporting system for drug shortages such as Belgium, the Netherlands, England, Italy, France, Germany and Spain were included in this study. Data about the characteristics of the drugs in shortage and the causes of the shortage were collected from publicly available online reporting systems. Descriptive analyses were performed. Results: Drug shortages included in the considered reporting systems can be characterized as branded, oral drugs that affect different disease domains. When considering essential medicines and oncology drugs, generic injectables are more involved. Causes for drug shortages are largely underreported. In case the cause is known, production problems take the lead. Conclusions: Reporting of drug shortages in Europe needs to be standardized and more transparency about the reasons for drug shortage is required to investigate the problem. A link between production problems and market attractiveness and market capacity is recognized to be at the root of drug shortages in U.S. Such insights are highly lacking in Europe. Monitoring of the effect of national and European health policies on the sustainability of the drug market is required to present fundamental solutions and to tackle the problem of drug shortages in Europe.

Peter, G. (2006). Tailoring the Strategies to Specific Shortages: Pneumococcal Conjugate Vaccine. Clinical Infectious Diseases, 42(Supplement 3), S138–S140. https://doi.org/10.1086/499593

Abstract: Less than 1 year after recommendations for the routine vaccination of infants with the newly licensed 7-valent polysaccharide-protein conjugate pneumococcal vaccine were issued in February 2000, shortages of the 7-valent polysaccharide-protein conjugate pneumococcal vaccine supply began to occur. A national shortage developed in 2001, involving both the public and private sectors, and it resulted in temporary recommendations to conserve vaccine supply for infants and young children at the highest risk for invasive disease. Multiple factors

contributed to this vaccine shortage, including demand that exceeded the expectations of the manufacturer and the need for compliance with the Good Manufacturing Practice of the US Food and Drug Administration. Of the possible strategies that might have averted this shortage, establishment of a vaccine stockpile is the most likely solution. However, establishing a stockpile for a newly licensed vaccine, such as 7-valent polysaccharide-protein conjugate pneumococcal vaccine, presents unique challenges. Improved communication with physicians and parents regarding changes in vaccine schedules also will promote better adherence to recommended changes and conservation of limited vaccine supplies during a shortage.

Plogsted, S., Adams, S. C., Allen, K., Breen, H. B., Cober, M. P., Greaves, J., ... Nutrition, the C. P. C. N. P. S. S. of the A. S. for P. and E. (2016). Parenteral Nutrition Electrolyte and Mineral Product Shortage Considerations. Nutrition in Clinical Practice, 31(1), 132–134. https://doi.org/10.1177/0884533615621550

No abstract available.

Plogsted, S., Adams, S. C., Allen, K., Cober, M. P., Greaves, J., Mogensen, K. M., ... Nutrition, A. S. for P. and E. (2016). Parenteral Nutrition Multivitamin Product Shortage Considerations. Nutrition in Clinical Practice, 31(4), 556–559. https://doi.org/10.1177/0884533616647718

No abstract available.

Pramyothin, P., Kim, D. W., Young, L. S., Wichansawakun, S., & Apovian, C. M. (2013). Anemia and Leukopenia in a Long-Term Parenteral Nutrition Patient During a Shortage of Parenteral Trace Element Products in the United States. Journal of Parenteral and Enteral Nutrition, 37(3), 425–429. https://doi.org/10.1177/0148607112463942

Abstract: Recently, drug shortages in the United States have affected multiple components of the parenteral nutrition (PN) solution. A 62-yearold patient with systemic sclerosis who was dependent on home PN due to intestinal dysmotility developed anemia and leukopenia approximately 4 months after parenteral copper was withheld from her PN solution due to drug shortages. The patient was not able to tolerate a sufficient amount of oral multivitamins with trace elements due to severe dysphagia. Her serum copper and ceruloplasmin concentrations were undetectable, confirming the diagnosis of severe copper deficiency. The hematological abnormalities promptly resolved with copper supplementation. This report emphasizes the importance of close monitoring for nutrient deficiencies during drug shortages and supplementing with oral or enteral nutrition when feasible, particularly in high-risk patients such as those with intestinal malabsorption or short bowel syndrome who are dependent on long-term PN

Printz, C. (2012). Medication shortages threaten cancer care. Cancer, 118(2), 289–291. https://doi.org/10.1002/cncr.27386

No abstract available.

Quadri, F., Mazer-Amirshahi, M., Fox, E. R., Hawley, K. L., Pines, J. M., Zocchi, M. S., & May, L.

(2015). Antibacterial Drug Shortages From 2001 to 2013: Implications for Clinical Practice. Clinical Infectious Diseases, 60(12), 1737–1742. https://doi.org/10.1093/cid/civ201

Abstract: Background. Previous studies have described drug shortages; however, there has been no comprehensive evaluation focusing on US antibacterial shortages. Methods. Drug shortage data from the University of Utah Drug Information Service database were analyzed, with a focus on antibacterial agents from 2001 to 2013. We used descriptive statistics to describe trends in drug shortages, analyze drug classes commonly affected, and investigate whether drugs experienced multiple periods of shortages. Results. One hundred forty-eight antibacterial drugs were on shortage over the 13-year study period, with 26 drugs still active on shortage as of December 2013. The median number of new shortages per year was 10 (interquartile range [IQR], 7). The number of drugs on shortage increased at a rate of 0.35 additional drugs every month (95% confidence interval, .22–.49) from July 2007 to December 2013 (P < .001). The median shortage duration was 188 days (IQR, 366.5). Twenty-two percent of drugs experienced multiple shortage periods. Conclusions. There were a substantial number of drug shortages from 2001 to 2013, with a dramatic rise in shortages since 2007. Shortages of agents used to treat multidrug-resistant infections are of concern due to continued transmission and limited treatment options.

Ralls, M. W., Blackwood, R. A., Arnold, M. A., Partipilo, M. L., Dimond, J., & Teitelbaum, D. H. (2012). Drug Shortage-Associated Increase in Catheter-Related Blood Stream Infection in Children. PEDIATRICS, 130(5), e1369–e1373. https://doi.org/10.1542/peds.2011-3894

Abstract: BACKGROUND: Ethanol lock therapy (ELT) has been shown to reduce the incidence of catheter-related blood stream infections (CRBSI) in intestinal failure (IF) patients. Dosing and frequency remains undefined. Scrutiny of pharmaceutical facilities by the Food and Drug Administration led to the voluntary shutdown of the sole supplier of ethanol, resulting in a nationwide shortage. To conserve supply, we reduced ELT frequency from a daily regimen. We examined the impact that reduction in ELT frequency had on CRBSI in pediatric IF patients. METHODS: We retrospectively reviewed our parenteral nutrition–dependent IF children. Primary outcome measure was CRBSI per 1000 catheter days after ELT frequency reduction. Data were compared (paired t test) to the same group over 1 year before ethanol shortage and to historical controls. RESULTS: During the shortage 13 outpatients received ELT. Eight met study criteria. Mean 6 SD age was 9.1 6 7.8 years. Mean CRBSI rate per 1000 catheter days was 0.7 6 1.3 before ELT shortage. This increased to 6.2 6 2.5 after frequency reduction (P , .001). This CRBSI rate was similar to historical IF children not on ELT (8.0 6 5.4). Seven children developed CRBSI after frequency reduction, 6 requiring hospitalization, 2 to the ICU. Mean length of stay (15.5 days) averaged $104,783(6 111,034) in hospital charges. Organisms included Gramnegatives (6), methicillin-resistant Staphylococcus aureus (1), and Candida spp (1). CONCLUSIONS: ELT frequency reduction resulted in complete failure in CRBSI prophylaxis. The nationwide shortage of this drug has been costly both financially and in patient morbidity.

Reed, B. N., Fox, E. R., Konig, M., Jackevicius, C. A., Masoudi, F. A., Rabinstein, A. A., & Page, R. L. (2016). The impact of drug shortages on patients with cardiovascular disease: causes, consequences, and a call to action. American Heart Journal, 175, 130–141. https://doi.org/10.1016/j.ahj.2016.02.004

Abstract: Shortages of cardiovascular drugs have become increasingly common, representing an ongoing public health crisis. Given few therapeutic alternatives to many of the drugs in short

supply, these shortages also pose a major challenge for cardiovascular care professionals. Although changes in the regulatory environment have led to some improvements in recent years, problems involving manufacturing processes remain the most common underlying cause. Because of the complex nature of drug shortages, sustainable solutions to prevent and mitigate them will require collaboration between regulatory agencies, drug manufacturers, and other key stakeholder groups. In this report, we describe the scope of the cardiovascular drug shortage crisis in the United States, including its underlying causes and the efforts currently being made to address it. Furthermore, we provide specific recommendations for how cardiovascular care professionals can be involved in efforts to limit the impact of drug shortages on patient care as well as policy changes aimed at preventing and mitigating them.

Reis, A. M., & Perini, E. (2008). Desabastecimento de medicamentos: determinantes, conseqüências e gerenciamento. Cien Saude Colet, 13(sSupl). Retrieved from http://www.scielo.br/pdf/csc/v13s0/a09v13s0

Abstract: The present study analyzes drug shortage as a problem reaching beyond the logistic aspect of the health field and discusses its consequences with respect to quality, safety and cost of health care delivery. The pharmaceutical supply chain and the factors that determine the distribution and availability of drugs are discussed. The contribution of the Pharmacy and Therapeutics Committee in preventing and managing drug shortage in health institutions is stressed and measures for drug shortage management are suggested. Finally it is emphasized that drugs should be considered health products rather than consumer goods and as such be given a different treatment by the supply chain.

Ruktanonchai, D., Lowe, M., Norton, S. A., Garret, T., Soghier, L., Weiss, E., … Centers for Disease Control and Prevention (CDC). (2014). Zinc deficiency-associated dermatitis in infants during a nationwide shortage of injectable zinc - Washington, DC, and Houston, Texas, 2012-2013. MMWR. Morbidity and Mortality Weekly Report, 63(2), 35–37.

Abstract: Injectable zinc, a vital component of parenteral nutrition (PN) formulations, has been in short supply in the United States since late 2012. In December 2012, three premature infants with cholestasis hospitalized in Washington, DC, experienced erosive dermatitis in the diaper area and blisters on their extremities, a condition that can be associated with zinc deficiency. All three infants were receiving PN because they had extreme cholestasis and were unable to be fed by mouth or tube. The PN administered to each infant was zinc deficient. Injectable zinc normally is added to PN for premature or medically compromised infants (e.g., those with cholestasis) by the hospital pharmacy because the amount of zinc needed by each patient differs; however, the pharmacy had run out of injectable zinc. No alternatives were available; other preparations of parenteral trace elements either contained insufficient zinc to meet infants' requirements or had the potential to cause trace element toxicity in infants with cholestasis (2). The dermatitis of one infant resolved after the patient was able to take nutrition by mouth. The other two infants were found to have low serum zinc levels. In January 2013, CDC was notified of four additional cases of zinc deficiency among infants with cholestasis who received zinc-deficient PN in a hospital in Houston, Texas. In collaboration with the Food and Drug Administration (FDA), the two hospitals obtained emergency shipments of injectable zinc. No additional cases were reported. Current injectable zinc supplies have been increasing as FDA collaborates with pharmaceutical companies to import emergency supplies. FDA is working to establish temporary backup sources should future shortages occur.

Salazar, E. G., Bernhardt, M. B., Li, Y., Aplenc, R., & Adamson, P. C. (2015). The impact of chemotherapy shortages on COG and local clinical trials: A report from the Children's Oncology Group: COG Chemotherapy Shortage Study. Pediatric Blood & Cancer, 62(6), 940–944. https://doi.org/10.1002/pbc.25445

Abstract: Background: Oncology drug shortage is associated with increased patient adverse events and decreased enrollment on clinical trials for adult patients; however, the impact of oncology drug shortages has not been well studied in children with cancer. Procedure: The Children's Oncology Group (COG) distributed a 5- item survey to 226 COG site-specific principal investigators (PI's) and 14-item survey to 161 COG pharmacists to gather data the impact of chemotherapeutic shortages on clinical trials and patient care. Results: The response rate was 66.4% (150/226) for PI's and 29.8% (48/161) for pharmacists. COG PI's reported daunorubicin (73%), methotrexate (56%), asparaginase/PEG-asparaginase (42%), doxorubicin (26%), thiotepa (21%), and cytarabine (20%) were most commonly in shortage, while COG pharmacists reported daunorubicin (80%), methotrexate (66%), vincristine (21%), thiotepa (41%), asparaginase/PEG-asparaginase (34%), and cytarabine (34%) were most commonly in shortage over the past two years. Pharmacists were twice as likely to report a shortage compared with PI's (OR 2.1, 95% CI: 1.6–2.7, P < 0.0001). Fifty percent (74/147) of COG PI's reported at least one patient enrolled on a clinical trial was impacted by drug shortage, and 66% (98/148) of COG PI's reported at least one patient had clinical care impacted by drug shortage. Conclusions: Chemotherapy shortages remain widespread across institutions, hinder clinical trials, and may contribute to adverse events in children with cancer. The increased frequency of chemotherapy shortages reported by pharmacists suggests that pharmacist efforts may mitigate negative impact chemotherapy shortages. Over half of pediatric institutions are implementing recommendations to address shortages, such as cross-institutional collaboration and center-level guidelines.

Schweitzer, S. O. (2013). How the US Food and Drug Administration Can Solve the Prescription Drug Shortage Problem. American Journal of Public Health, 103(5), e10–e14. https://doi.org/10.2105/AJPH.2013.301239

Abstract: Drug shortages are threatening care quality and cost-containment efforts. I describe the pharmaceutical marketplace changes that have caused the problem, and propose new policies to solve it, through changing incentives for producers and purchasers. I propose a grading scheme for the Food and Drug Administration when it inspects manufacturing facilities in the United States and abroad. The inspections' focus would change from closing unsafe plants to improving production process quality, reducing the likelihood that plants will be closed—the most frequent cause of drug shortages.

Sheth, H. S., Verrico, M. M., Skledar, S. J., & Towers, A. L. (2005). Promethazine Adverse Events after Implementation of a Medication Shortage Interchange. Annals of Pharmacotherapy, 39(2), 255–261. https://doi.org/10.1345/aph.1E361

Abstract: BACKGROUND: Prochlorperazine and droperidol were commonly used antiemetics at the University of Pittsburgh Medical Center–Presbyterian Hospital until a shortage of prochlorperazine occurred and a black box warning was added to droperidol prescribing information. Subsequently, promethazine was selected as the approved intravenous antiemetic for therapeutic interchange in December 2001. Promethazine use and adverse drug events

(ADEs) were investigated following review of a serious ADE that identified promethazine use as a probable contributing factor. OBJECTIVE: To illustrate ADEs associated with promethazine and characterize high-risk patients. METHODS: An ADE database analysis identified promethazine ADEs reported from 2000 to 2003. Promethazine utilization and ADEs were compared with those of other antiemetics during the pre- and post-interchange periods. RESULTS: Promethazine utilization increased significantly during the post-interchange period compared with all other antiemetics (p< 0.001). Promethazine ADEs increased from one event during the pre-interchange period to 13 events during the post-interchange period. Causality assessment using the Naranjo algorithm ranged from possible to probable. The promethazine ADE rate per 10 000 doses was significantly higher than the combined ADE rate for all other antiemetics (p < 0.001; incident rate ratio [IRR] 4.32). Elderly patients (aged ≥65 y) experienced more promethazine ADEs than younger patients (p = 0.005; IRR 4.68). Concurrent use of opioids and/or sedating drugs contributed to promethazine ADEs in 11 of 14 (78.6%) patients. CONCLUSIONS: Geriatric status is a significant risk factor for promethazine ADEs. Concomitant use of sedating drugs may further increase the risk for ADEs. Therapeutic interchange programs should be monitored for both ADEs and utilization.

Singleton, R., Chubbs, K., Flynn, J., Kaposy, C., Peckham, G., Penney, J., & Pullman, D. (2013). From Framework to the Frontline: Designing a Structure and Process for Drug Supply Shortage Planning. Healthcare Management Forum, 26(1), 41–45. https://doi.org/10.1016/j.hcmf.2012.11.003

Abstract: Drug shortages are not new; they have been managed through conservation, procurement of alternatives, and redistribution of stock. The Sandoz shortage in 2012 has caused a radical reduction of generic injectables. In Newfoundland and Labrador, our response has led to the development of the framework, structure, and process outlined in this paper. The efforts have eased the concerns of clinicians and leaders, as they are aware of the decision-making resource for situations of drug and technology shortage.

Sirrs, S. (2011). The Fabrazyme shortage—A call to action for metabolic physicians. Molecular Genetics and Metabolism, 102(1), 4–5. https://doi.org/10.1016/j.ymgme.2010.11.002

Abstract: The recent shortages of enzyme replacement therapy for Fabry disease have highlighted areas of vulnerability for patients who require this treatment. Guidelines on allocation of limited stock of enzyme replacement therapy are of use for clinicians dealing with the current shortages. However, the community of metabolic physicians must advocate for changes that will minimize the impact of future drug shortages for their patients with lysosomal storage diseases.

Storey, M. A., Weber, R. J., Besco, K., Beatty, S., Aizawa, K., & Mirtallo, J. M. (2016). Evaluation of Parenteral Nutrition Errors in an Era of Drug Shortages. Nutrition in Clinical Practice, 31(2), 211–217. https://doi.org/10.1177/0884533615608820

Abstract: Background:Ingredient shortages have forced many organizations to change practices or use unfamiliar ingredients, which creates potential for error. Parenteral nutrition (PN) has been significantly affected, as every ingredient in PN has been impacted in recent years. Materials and Methods: Ingredient errors involving PN that were reported to the national anonymous MedMARx database between May 2009 and April 2011 were reviewed. Errors were categorized by ingredient, node, and severity. Categorization was validated by experts in

medication safety and PN. A timeline of PN ingredient shortages was developed and compared with the PN errors to determine if events correlated with an ingredient shortage. This information was used to determine the prevalence and change in harmful PN errors during periods of shortage, elucidating whether a statistically significant difference exists in errors during shortage as compared with a control period (ie, no shortage). Results: There were 1311 errors identified. Nineteen errors were associated with harm. Fat emulsions and electrolytes were the PN ingredients most frequently associated with error. Insulin was the ingredient most often associated with patient harm. On individual error review, PN shortages were described in 13 errors, most of which were associated with intravenous fat emulsions; none were associated with harm. There was no correlation of drug shortages with the frequency of PN errors. Conclusion: Despite the significant impact that shortages have had on the PN use system, no adverse impact on patient safety could be identified from these reported PN errors.

Thoma, B. N., Li, J., McDaniel, C. M., Wordell, C. J., Cavarocchi, N., & Pizzi, L. T. (2014). Clinical and Economic Impact of Substituting Dexmedetomidine for Propofol due to a US Drug Shortage: Examination of Coronary Artery Bypass Graft Patients at an Urban Medical Centre. PharmacoEconomics, 32(2), 149–157. https://doi.org/10.1007/s40273-013-0116-8

Abstract: BACKGROUND: Propofol has reduced healthcare costs in coronary artery bypass graft (CABG) surgery patients by decreasing post-operative duration of mechanical ventilation. However, the US shortage of propofol necessitated the use of alternative agents. OBJECTIVE: This study sought to evaluate clinical and economic implications of substituting dexmedetomidine for propofol in patients undergoing CABG surgery. METHODS: This was a retrospective cohort study. Patients undergoing isolated, elective CABG surgery and sedated with either propofol or dexmedetomidine during the study period were included. The cohorts were matched 1:1 based on important characteristics. The primary outcome was the number of patients achieving a post-operative duration of mechanical ventilation ≤6 h. Secondary outcomes were post-operative intensive care unit (ICU) length of stay (LOS) ≤48 h, total post-operative LOS ≤5 days, the need for adjunctive opioid therapy and associated cost savings. Variables recorded included patient demographics, co-morbid medical conditions, health risks, sedation drug doses, post-operative medical complications and sedation- related adverse events. Univariate and multivariate analyses were completed to examine the relationship between these covariates and post-operative LOS. The cost analysis consisted of examination of the net financial benefit (or cost) of choosing dexmedetomidine versus propofol in the study population, with utilisation observed in the study converted to costs using institutional data from the Premier database. RESULTS: Eighty-four patients were included, with 42 patients per cohort. Mechanical ventilation duration ≤6 h was achieved in 24 (57.1 %) versus 7 (16.7 %) in the dexmedetomidine and propofol cohorts, respectively (p < 0.001). More patients treated with dexmedetomidine achieved ICU LOS ≤48 h (p < 0.05) and total hospital LOS ≤5 days (p < 0.05), as compared with the propofol group. Multivariate analysis revealed that having one or more post-operative medical complication was the most significant predictor of increased post-operative LOS, whereas choosing dexmedetomidine was also significant in terms of reduced post-operative LOS. The estimated net financial benefit of choosing dexmedetomidine versus propofol was US$2,613 per patient (year 2012 value). CONCLUSIONS: Findings suggest that use of dexmedetomidine as an alternative to propofol for sedation of CABG patients post-operatively contributes to reduced mechanical ventilation time, ICU LOS and post-operative LOS. Higher drug costs resulting from the propofol shortage were offset by savings in post-operative room

and board costs. Additional savings may be possible by preventing medical complications to the extent possible.

Tolia, V. N., Murthy, K., McKinley, P. S., Bennett, M. M., & Clark, R. H. (2014). The Effect of the National Shortage of Vitamin A on Death or Chronic Lung Disease in Extremely Low-Birth-Weight Infants. JAMA Pediatrics, 168(11), 1039. https://doi.org/10.1001/jamapediatrics.2014.1353

Abstract: IMPORTANCE Prophylactic vitamin A supplementation has been shown to reduce the incidence of chronic lung disease or death in extremely low-birth-weight infants. Beginning in 2010, a national shortage reduced the supply of vitamin A available. OBJECTIVE: To estimate the association between vitamin A supplementation and death or chronic lung disease in the context of the recent drug shortage. Intercenter variability in vitamin A use was assessed secondarily. DESIGN, SETTING, AND PARTICIPANTS: Retrospective cohort study of 7925 infants with birth weights between 401 and 1000 g who were cared for in US neonatal intensive care units managed by the Pediatrix Medical Group. Infants were discharged between January 1, 2010, and June 30, 2012, and data were collected from the Pediatrix Clinical Data Warehouse. Infants who had major congenital anomalies, died during the first 3 days of life, or had missing data were excluded from the analysis. EXPOSURES: Vitamin A supplementation. MAIN OUTCOMES AND MEASURES: The primary outcome was either death before hospital discharge or chronic lung disease, defined as receiving any respiratory support at 36 weeks' corrected gestational age. RESULTS: Of the 6210 eligible infants, 3011 (48.5%) experienced the primary outcome. Those who received vitamin A were more immature and more likely to receive mechanical ventilation during the first 3 days of life. During the study period, vitamin A supplementation significantly decreased (27.2% to 2.1%); however, the primary outcome was similar (48.4% to 49.5%; P = .40). Vitamin A was unrelated to death or chronic lung disease in unadjusted or multivariable analyses (relative risk [RR], 0.97; 95% CI, 0.91-1.03; P = .32) when demographic and clinical information were considered. After classifying centers by vitamin A use, the center of birth was significantly associated with the outcome, with birth in low- and medium- use centers related to a reduced likelihood of death or chronic lung disease. CONCLUSIONS AND RELEVANCE: The occurrence of death or chronic lung disease appears unaffected by the recent shortage of vitamin A. However, the center of birth appears to be an important risk factor for these infants' outcomes.

Tomlin, S. (2016). Where have all the medicines gone? Archives of Disease in Childhood, 101(7), 648–649. https://doi.org/10.1136/archdischild-2014-307907

No abstract available.

Traynor, K. (2011). Drug shortage solutions elude stakeholders. American Journal of Health-System Pharmacy: AJHP: Official Journal of the American Society of Health-System Pharmacists, 68(22), 2106, 2108. https://doi.org/10.2146/news110074

No abstract available.

Valgus, J., Singer, E. A., Berry, S. R., & Rathmell, W. K. (2013). Ethical Challenges: Managing Oncology Drug Shortages. Journal of Oncology Practice, 9(2), e21–e23. https://doi.org/10.1200/JOP.2012.000779

Abstract: This vignette highlights the ethical issues surrounding restricted access to oncology drugs caused by shortages., This vignette highlights the ethical issues surrounding restricted access to oncology drugs caused by drug shortages. A review of selected literature and a framework for creating institutional guidelines for reacting to shortage is provided.

Vogel, L. (2012). Online drug shortage registry imited in application. CMAJ : Canadian Medical Association Journal, 184(3), E165–E166. https://doi.org/10.1503/cmaj.109-4100

No abstract available.

Wenzel, R. (2015). Drug Shortages and Tipping Points. Headache: The Journal of Head and Face Pain, 55(9), 1294–1295. https://doi.org/10.1111/head.12689

No abstract available.

Woodcock, J., & Wosinska, M. (2012). Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages. Clinical Pharmacology & Therapeutics. https://doi.org/10.1038/clpt.2012.220

Abstract: Over the past few years, an increasing number of critically needed medicines have been in short supply. Using economic theory to frame the drug-shortage problem, this paper explores why and how manufacturing-quality problems could combine with other economic and technological factors to result in shortages of generic sterile injectable drugs. The fundamental problem we identify is the inability of the market to observe and reward quality. This lack of reward for quality can reinforce price competition and encourage manufacturers to keep costs down by minimizing quality investments. The US Food and Drug Administration's (FDA's) need to use its regulatory flexibility, on behalf of patients, to avoid shortages of medically necessary drugs may further strengthen the incentive to "push the envelope" on quality. These dynamics may have produced a market situation in which quality problems have become sufficiently common and severe to result in drug shortages.

Wuerz, T. C., Bow, E. J., & Seftel, M. D. (2013). Potential consequences of essential drug shortages in Canada: Brain abscess due to Nocardia farcinica associated with dapsone prophylaxis for Pneumocystis jirovecii pneumonia. The Canadian Journal of Infectious Diseases & Medical Microbiology, 24(3), 159–161.

Abstract: In 2012, Canadian pharmacies experienced a shortage of trimethoprim-sulfamethoxazole tablets. Drug shortages may result in unintended clinical consequences such as infection with pathogens against which the alternative medication is ineffective. This is highlighted in the present article, which describes a case of brain abscess due to Nocardia species that developed while receiving dapsone as an alternative for prophylaxis against Pneumocystis jirovecii pneumonia in a highly immune-suppressed patient. Clinicians should be cognizant of these issues when prescribing alternative agents.

* For the purposes of this review, we have established three categories to describe the state of the literature: thin, considerable, and rich.

- *Thin: There are relatively few papers and/or there are not many recent papers and/or there are clear gaps*
- *Considerable: There are several papers and/or there are a handful of recent papers and/or there are some clear gaps*
- *Rich: There is a wealth of papers on the topic and/or papers continue to be published that address this issue area and/or there are less obvious gaps*

Scope: While many of these issues can touch a variety of sectors, this review focuses on medicines. The term medicines is used to cover the category of health technologies, including drugs, biologics (including vaccines), and diagnostic devices.

Disclaimer: The research syntheses aim to provide a concise, comprehensive overview of the current state of research on a specific topic. They seek to cover the main studies in the academic and grey literature, but are not systematic reviews capturing all published studies on a topic. As with any research synthesis, they also reflect the judgments of the researchers. The length and detail vary by topic. Each synthesis will undergo open peer review, and be updated periodically based on feedback received on important missing studies and/or new research. Selected topics focus on national and international-level policies, while recognizing that other determinants of access operate at sub-national level. Work is ongoing on additional topics. We welcome suggestions on the current syntheses and/or on new topics to cover.