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ASPE REPORT

Impact of Drug Shortages on Patients in the United States: A Case Study of Three Drugs

The Office of the Assistant Secretary for Planning and Evaluation (ASPE)
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Acronyms

The following acronyms are mentioned in this report and appendix.

ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
APIs	Active Pharmaceutical Ingredients
CMS	Centers for Medicare and Medicaid Services
Dx	Pre-adjudicated Open-Source Medical Professional and Institutional Claims (IQVIA)
FDA	U.S. Food and Drug Administration
FPL	Federal poverty level
GPO	Group Purchasing Organization
HCPCS	Healthcare Common Procedure Coding System
ICD-10-CM	International Classification of Diseases tenth version, Clinical Modification
IQVIA	I (IMS Health), Q (Quantiles), and VIA (by way of)
NDCs	National Drug Codes
NPPES	National Plan and Provider Enumeration System
PBL	Porton Biopharma Limited
SEER	Surveillance, Epidemiology, and End Results

Executive Summary

Drug shortages are a persistent problem that can cause substantial disruption in patient treatment regimens and adversely impact a patient's health. Prior studies have demonstrated that drug shortages can have severe consequences for patients, including high costs, delayed care, and potential medication errors or unintended side effects when using alternative or unfamiliar drugs.[1,2,3]

There are many causes of drug shortages including disruptions to the supply chain, sudden increases in demand for a drug, and manufacturing or quality issues. Many of the drugs in shortage are generic drugs, which are typically older and have lower financial margins. Many of these generic drugs are also sterile injectables, which are complex to manufacture and are critical to treat many life-threatening conditions, including cancer.[4] Drug shortages within the injectable oncology space are particularly concerning as patients with cancer are vulnerable to increased morbidity and mortality when treatment is interrupted or delayed, and there are often few substitutes for these drugs.

In a competitive market, economic theory suggests that when there is an increase in demand for a drug, there would be an associated increase in price for the drug in shortage resulting in an increase in supply, which would help to resolve the shortage. Further, if there is a product considered to be the same as the drug in shortage (substitute), then the price of the substitute drug would decrease and the use of the substitute drug increase. Motivated by this general framework, this report presents findings on the associated changes on patient utilization and service charges, which is our proxy measure for cost or price, with shortages of three drugs that are used as a case study.[4]

Our sample was based on data available to ASPE at the time of this analysis and included heparin, asparaginase, and nelarabine and their substitutes (Exhibit E1). Substitute drugs were identified by clinicians based on the sample of shortage cases and treatment alternatives that were either primarily pharmacy-dispensed or physician-dispensed. The underlying assumption was that the substitutes would be products in the same therapy class but not necessarily in the same drug class. The drugs that were selected for this analysis were all injectables that are primarily administered in a hospital or office-based setting. The drugs in the sample are used to treat life-threatening conditions and their shortages began between 2016 and 2020, the period of time for which data were available at the time this analysis was conducted. Two of the drugs, asparaginase and nelarabine, are used in pediatric patients with leukemia

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[1] Shukar, S., Zahoor, F., Hayat, K., Saeed, A., Gillani, A. H., Omer, S., ... & Yang, C. (2021). Drug shortage: causes, impact, and mitigation strategies. *Frontiers in pharmacology*, *12*, 693426.

[2] 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.

[3] Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health & Human Services. Impact of Drug Shortages on Consumer Costs. May 2023. https://aspe.hhs.gov/reports/drug-shortages-impacts-consumer-costs

[4] Generally, a charge is the dollar amount a health care provider sets for services rendered before negotiating any discounts; the charge can be different from the actual amount paid. To patients, costs usually represent the amount they have to pay out-of-pocket for health care services, which will vary based on the type of insurance coverage. IQVIA defines "service charge" as the charges related to a medical service. In this analysis, "service charges" are standardized to be total service charge divided by the count of drugs.

and the other, injectable heparin,[5] is used to prevent or treat certain blood vessel, heart, and lung conditions as well as to prevent blood clotting during certain surgeries and may be part of the treatment regimen for patients with cancer. We also examine utilization and cost for a select number of drugs that are considered clinical alternatives (substitutes) for each drug in shortage. The research questions are:

- How many patients are impacted by each shortage?
- What are the key demographic characteristics of the patients affected by the shortages?
- How do patient utilization and costs change before, during, and after a shortage?
- How do patient utilization and costs of an alternative drug change before, during, and after the shortage of the selected drug?

Exhibit E1: List of Shortage and Substitute Drugs, Shortage Period, and Reason for Shortage

Drug name	Shortage Period	Substitute Drug Name	Uses	Reason for Shortage
Asparaginase	10/14/2016 - 08/2021*	Pegaspargase	Suppresses tumors in persons with leukemia; lowers the concentration of the amino acid asparagine	Supply disruption due to ongoing manufacturing issues and capacity constraints
Nelarabine	10/30/2018 - 01/2020*	Cladribine Clofarabine Fludarabine	Targets T-cells in persons with leukemia	Increased demand**
Heparin	11/14/2017 - ongoing*	Bivalirudin Lepirudin	Anticoagulant; commonly used for patients with cancer and other conditions as prophylaxis or treatment of venous thromboembolic events	Increased demand and manufacturing delays

Source: Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Notes: * Our data for utilization and cost run through 2020. As of March 2024, heparin had been in shortage since 2017 and the shortage of asparaginase ended in August 2021.** It is possible that this increase in nelarabine demand occurred after a 2018 study demonstrated the effectiveness of the drug against T-cell acute lymphoblastic leukemia.

Study Methods

We examined utilization of these drugs before, during, and after shortages to determine whether there were differences in the unique number of patients taking the drug, the units administered, or the service charge. We conducted a similar analysis for the alternative treatments for the drugs of interest.

[5] Heparin is a blood thinner. There are two types of heparins widely used, unfractionated heparin (UFH) and low molecular weight heparin (LMWH). The shortage of heparin examined in this analysis was associated with unfractionated heparin (heparin sodium) or injectable heparin, which for brevity we refer to as heparin throughout the rest of this analysis. We do not discuss LMWH heparin due to data and methodological considerations; see “Background on Selected Drugs” for additional details.

This study was based on analysis of IQVIA Medical Claims (Dx) data for 2016-2020. The Dx data included pre-adjudicated all-payer claims generated by office-based physicians and specialists. We identified the drugs of interest, asparaginase, nelarabine, and heparin, and their substitutes, using Healthcare Common Procedure Coding System (HCPCS) codes listed in the procedure code field for each claim line item. We selected patients in the Dx claims data by using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes for cancer or neoplasms (new or abnormal growth of tissue). We note that we assumed that patients meeting the criteria were those seeking treatment for cancer and that we were not able to observe those patients who were unable to access a drug due to the shortage, cost, or any other reason. We also used the U.S. Food and Drug Administration (FDA) List of Drug Shortages which was downloaded in March 2020 to identify the start and end of the shortages as well as their cause.

We analyzed the data at both the drug and patient level. The drug level analysis examined the count of all current patients and new patients (those with a first claim for a given drug in a given month) for each drug. We also examined the total units administered and service charge for each drug over time. At the patient level, we examined demographic characteristics, such as age, gender, and race/ ethnicity, and explored whether patients switched to substitute drugs during the shortage, dropped the medication, or maintained the drug with a change in the service charge.

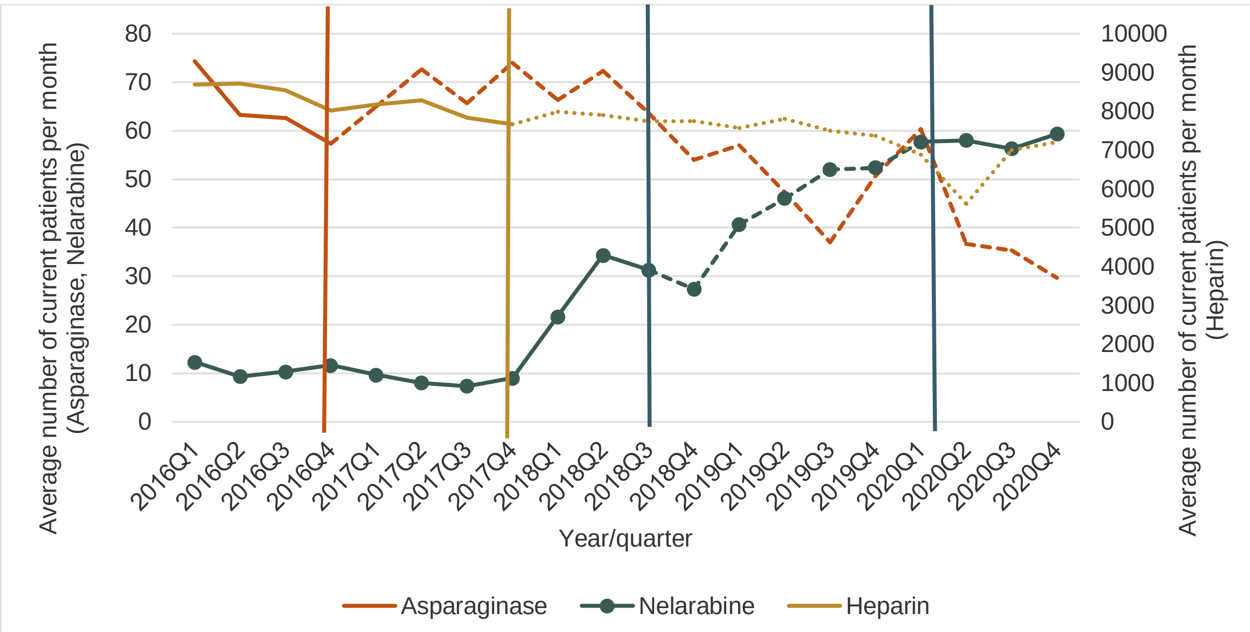
Results

As illustrated in Exhibit E2, each of the three analyzed drugs had a different pattern of change in the number of patients using the drug across the pre-shortage, shortage, and post-shortage periods. For asparaginase, the number of patients using the drug declined between the pre-shortage and post-shortage periods, despite substantial quarter by quarter variation during the shortage period. For nelarabine, the number of patients using the drug was stable pre-shortage but started to significantly increase three months before the shortage began, a trend that continued through the shortage period. After the shortage, the number of patients using nelarabine stabilized. For heparin, the number of patients using heparin declined slightly during the shortage period.

We found no clear pattern in the change in units administered or service charges during the shortage period for the selected drugs. Although there was quarter-to-quarter fluctuation in the number of units administered and service charges during the shortage period of asparaginase, we observed a slight increase in the units administered and service charges starting in 2020 when the shortage began to be resolved. The usage of asparaginase paralleled that of its substitute drugs, i.e., use declined for both drugs during the period of analysis. The usage and service charges of nelarabine decreased significantly about one year before the drug was officially declared to be in shortage, stabilizing more than two years after the shortage began and at levels that were almost half that of the pre-shortage period. The usage of some, but not all, the substitute drugs for nelarabine increased during the period of analysis. Furthermore, we observed a steady increase in the usage of heparin, which coincided with a temporary increase in the use of its substitute drug. We also observed a significant increase in the service charges of heparin during the period of analysis. These results suggest that the market for these drugs did not respond to shortages in the manner that theory suggests in that supply did not increase to meet demand, and that there was little substitution towards the identified list of drugs classified as potential alternatives.

Further, the data showed that the demographic characteristics of those affected by the shortage vary by drug. For example, most of the patients affected by a shortage of asparaginase and nelarabine were males under the age of 18. By contrast, most users of heparin were females over the age of 40.

Exhibit E2 - Average Number of Current Patients Taking Each Shortage Drug, 2016-2020



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Notes: The vertical lines identify the end and start of the shortage period for each drug. As of March 2024, heparin was still in shortage since November 2017. The shortage period for asparaginase was from October 2016 to August 2021. The shortage period for nelarabine was from October 2018 to January 2020.

Due to the characteristics of IQVIA Dx data, there were several limitations that affected our analysis. Since IQVIA Dx was composed of pre-adjudicated claims, the dataset did not include the final payment amount and it was not possible to identify claims that were eventually declined. There were also some claims with missing or negative values for patient birth year, gender, and payment. While our analysis allowed us to observe changes in the number of patients, charges, and supplied units across the pre-shortage, shortage, and post-shortage periods, the study data did not allow us to estimate the number of patients that were unable to access a drug due to the shortage. Further, some of the analyses had small sample sizes that introduce uncertainty and limit generalizability of the results.

Conclusion

The analysis did not reveal conclusive evidence regarding the use and price of three select drugs that are indicated for cancer care and that entered shortage status during 2016-2020. We also observed disparate results in the use of substitute drugs. Use of the drug in shortage and its substitutes appears to depend not just on the reason of the shortage (increase in demand vs manufacturing delay), but also on the number of manufacturers and substitutes available, and the effectiveness of the alternative drug relative to the drug in shortage. The analysis also showed that the duration of these shortages can be long-lasting, with some shortages lasting almost five years. The results suggest that larger studies that include more drugs and more data are needed to better understand the underlying dynamics and characteristics of shortages and their impacts. While the analysis in this study allowed us to observe changes in the number of patients, charges, and supplied units across the pre-shortage, shortage, and post-shortage periods, the study data did not allow us to estimate the number of patients that were unable to access treatment drugs due to the shortages. Our analysis also had several data limitations including small sample size and missing data that limit the interpretation of the results. Future research could improve on this study by examining cohorts of patients longitudinally or by examining the impact at the National Drug Code (NDC) level rather than at the active ingredient level, as was done in this study.

Chapter 1. Background and Analysis

In this chapter, we provide a background on drug shortages, an explanation of the medications selected for our research, and a description of the methodology used in our analysis.

Background on Drug Shortages

Drug shortages can cause substantial disruption in the treatment regimen of patients using the medications and can adversely impact a patient's health outcomes.[6,7] Drug shortages can have severe consequences for patients, including delayed care, increased costs, medication errors, and adverse events, such as disability and death.[8,9,10] One recent study reported that physicians working in underserved communities were more likely to report negative outcomes from drug shortages than physicians who do not serve vulnerable communities,[11] but there has been little systematic examination of the demographic characteristics of the patients affected.

Drug shortages may be triggered by supply chain disruptions and increased demand, among other reasons.[7,12,13] Generic drugs with few manufacturers are at particular risk of shortage. The supply of generic sterile injectables is further susceptible to shortages because of a history of low investments in the specialized equipment necessary to produce them.[12] Drug shortages within the injectable oncology space are particularly concerning because disruptions or alterations to chemotherapy regimen may increase the risk of cancer progression and death.[12,14]

Some have cited that manufacturing complexity and regulatory requirements for pharmaceutical drugs may make it difficult to attract new entry or increase production to levels necessary to resolve shortages quickly.[15,16] Among other actions, the U.S. Food and Drug Administration (FDA) can take a number of

[6] U.S. Food and Drug Administration (FDA). (2020). Report to Congress: Drug Shortages for Calendar Year 2020. Accessed July 31, 2022. https://www.fda.gov/media/150409/download

[7] Ventola, C. L. (2011). The drug shortage crisis in the United States: causes, impact, and management strategies. *Pharmacy and Therapeutics*, *36*(11), 740.

[8] Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health & Human Services. Impact of Drug Shortages on Consumer Costs. May 2023. https://aspe.hhs.gov/reports/drug-shortages-impacts-consumer-costs

[9] Phuong, J. M., Penm, J., Chaar, B., Oldfield, L. D., & Moles, R. (2019). The impacts of medication shortages on patient outcomes: a scoping review. *PloS one*, *14*(5), e0215837.

[10] 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.

[11] The United States Pharmacopeial Convention (USP). (2021). U.S. Physician Survey. State of the Medicines Supply Chain & Impact of COVID-19. https://go.usp.org/hcp-survey

[12] Shukar, S., Zahoor, F., Hayat, K., Saeed, A., Gillani, A. H., Omer, S., ... & Yang, C. (2021). Drug shortage: causes, impact, and mitigation strategies. *Frontiers in pharmacology*, *12*, 693426.

[13] Link, M. P., Hagerty, K., & Kantarjian, H. M. (2012). Chemotherapy drug shortages in the United States: genesis and potential solutions. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *30*(7), 692-694.

[14] McBride, A., Holle, L. M., Westendorf, C., Sidebottom, M., Griffith, N., Muller, R. J., & Hoffman, J. M. (2013). National survey on the effect of oncology drug shortages on cancer care. *American journal of health-system pharmacy*, *70*(7), 609-617.

[15] U.S. Food and Drug Administration (FDA). (2020). Report to Congress: Drug Shortages for Calendar Year 2020. Accessed July 31, 2022. https://www.fda.gov/media/150409/download

[16] Ventola, C. L. (2011). The drug shortage crisis in the United States: causes, impact, and management strategies. *Pharmacy and Therapeutics*, *36*(11), 740.

actions to mitigate or prevent shortages which include expediting FDA's inspections and reviews of submissions by affected manufacturers attempting to restore production and expediting FDA's inspections of manufacturing plants and reviews of submissions from competing entities that may be able to start new production or increase production of products in shortage.

Background on Selected Drugs

Asparaginase, nelarabine and heparin are injectable drugs that are administered in clinical settings for the treatment of patients with cancer and associated medical complications or comorbidities. These three medications have experienced shortages over the past decade.[14,17] The specialty nature of these sterile injectables and the facilities required to manufacture them are barriers to entry for potential new manufacturers, which means that it may take substantial time to recover from a supply disruption.[12] For example, in the case of the shortage of asparaginase, due to a supply disruption, it took almost five years for the shortage to be resolved. Exhibit 1 describes asparaginase, nelarabine and heparin, the number of national drug codes (NDCs) associated with each drug, the shortage periods for each drug, potential alternatives to the drug in shortage, the uses for the drug in shortage, and reasons for the shortage.

Exhibit 1: Characteristics of Select Drugs in Shortage Used in Treatment of Patients with Cancer

Drug name (Number of NDCs)	Shortage Period[1]	Substitute Drug Name[5]	Uses	Reason for Shortage
Asparaginase (2)	10/14/2016 - 8/2021[2]	Pegaspargase	Suppresses tumors in persons with leukemia; lowers the concentration of the amino acid asparagine	Supply disruption due to ongoing manufacturing issues and capacity constraints
Nelarabine (4)	10/30/2018 - 1/7/2020[2]	Cladribine Clofarabine Fludarabine	Targets T-cells in persons with leukemia	Increased demand[3]
Heparin[4] (421)	11/14/2017 – ongoing[2]	Bivalirudin Lepirudin	Anticoagulant; commonly used for patients with cancer and other conditions as prophylaxis or treatment of venous thromboembolic events	Increased demand and manufacturing delays

Note: 1. Shortage periods were derived using the following steps: a) Extracted a point-in-time extract from the FDA Drug Shortage Database (downloaded March 2020) and b) Modified the extract to unpack multiple NDCs and remove discontinuations. 2. As of March 2024, heparin was still in shortage since November 2017. The shortage period for asparaginase was from October 2016 to August 2021. The shortage period for nelarabine was from October 2018 to January 2020. 3. It is possible that this increase in nelarabine demand occurred after a 2018 study demonstrated the effectiveness of the drug against T-cell acute lymphoblastic leukemia. 4. The shortage of heparin involved only unfractionated heparin (heparin sodium) so the counts of NDCs available include unfractionated heparin only. 5. Alternative products or substitutes were determined by clinicians assuming that alternatives within the same drug class may not be available.

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[17] DeCamp, M., Joffe, S., Fernandez, C. V., Faden, R. R., & Unguru, Y. fnm Lingua:: EN:: Titlecase,"Chemotherapy drug shortages in pediatric oncology: a consensus statement,". *Pediatrics*, *133*(3), e716-e724.

Asparaginase is a chemotherapy drug that lowers the concentration of the amino acid asparagine circulating within the body, which can be crucial in suppressing the formation of tumors in persons with leukemia.[18] In particular, acute lymphoblastic leukemia (ALL), a blood cancer in children, is best managed when leukemia cells are deprived of asparagine.[19] As of March 2024, there are two approved products available but at the time the shortage began there was only one manufacturer of asparaginase. Manufacturing quality issues and a rise in demand for the drug have been cited as the reasons for the shortage of asparaginase.[20] Asparaginase has become more popular relative to its substitutes due to its diminished cytotoxicity, meaning it is not as toxic to other, living cells in the body, which can help cancer patients heal faster. Pegasparginase has been identified as a potential substitute but more evidence is needed to support its status.[21,22]

Similarly, nelarabine is utilized in the treatment of ALL, though it specifically targets the T-cells responsible for tumors.[23] Nelarabine is a pro-drug (a drug that needs to be activated in the body),[23] which is rapidly converted to a molecule (ara-G) with T-cell selective cytotoxicity, which means that the drug has the ability to selectively target and inhibit the infecting T-cells while minimizing the damage to the cancer patient. Ultimately this is the most effective therapy for patients with hematologic malignancies (cancers that affect the blood, bone marrow, and lymph nodes). While the substitutes for nelarabine—namely cladribine, clofarabine, and fludarabine—do not share the same indication as that of nelarabine, some evidence suggests nelarabine may have the potential for a better safety profile.[25,24] In 2018 a study demonstrated the effectiveness of nelarabine against T-cell acute lymphoblastic leukemia, which may have contributed to the increase in demand for nelarabine.[25] Further research is needed to understand the extent to which these drugs can be fully substituted for nelarabine, especially in pediatric and young adult patients.

Discovered in 1916, heparin has been used as an anticoagulant since 1935 and its demand continues to rise for the treatment of cardiovascular disease, thrombosis, and recently for the treatment of COVID-19 associated thromboembolic disease. While heparin is primarily used as an anticoagulant (blood thinner),

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[18] Salzer, W., Bostrom, B., Messinger, Y., Perissinotti, A. J., & Marini, B. (2018). Asparaginase activity levels and monitoring in patients with acute lymphoblastic leukemia. *Leukemia & Lymphoma*, *59*(8), 1797-1806.

[19] Costa-Silva, T. A., Costa, I. M., Biasoto, H. P., Lima, G. M., Silva, C., Pessoa, A., & Monteiro, G. (2020). Critical overview of the main features and techniques used for the evaluation of the clinical applicability of L-asparaginase as a biopharmaceutical to ommunittreat blood cancer. *Blood Reviews*, *43*, 100651.

[20] Jensen L, Wheeler M. Asparaginase Erwinia Chrysanthemi. (2018). Drug Shortages. Accessed August 23, 2022.https://www.drugs.com/drug-shortages/asparaginase-erwinia-chrysanthemi-482;

[21] Medawar, C. V., Mosegui, G. B. G., Vianna, C. M. D. M., & Costa, T. M. A. D. (2020). PEG-asparaginase and native Escherichia coli L-asparaginase in acute lymphoblastic leukemia in children and adolescents: a systematic review. *Hematology, transfusion and cell therapy*, *42*, 54-61.

[22] Verma, A., Chen, K., Bender, C., Gorney, N., Leonard, W., & Barnette, P. (2019). PEGylated E. coli asparaginase desensitization: an effective and feasible option for pediatric patients with acute lymphoblastic leukemia who have developed hypersensitivity to pegaspargase in the absence of asparaginase Erwinia chrysanthemi availability. *Pediatric Hematology and Oncology*, *36*(5), 277-286.

[23] Kadia, T. M., & Gandhi, V. (2017). Nelarabine in the treatment of pediatric and adult patients with T-cell acute lymphoblastic leukemia and lymphoma. *Expert review of hematology*, *10*(1), 1-8.

[24] Reilly, K. M., & Kisor, D. F. (2009). Profile of nelarabine: use in the treatment of T-cell acute lymphoblastic leukemia. *OncoTargets and therapy*, 219-228.

[25] Dunsmore, K. P., Winter, S., Devidas, M., Wood, B. L., Esiashvili, N., Eisenberg, N., ... & Hunger, S. (2018). COG AALL0434: A randomized trial testing nelarabine in newly diagnosed t-cell malignancy.

it is also being studied for its potential to regulate cancer cell growth .[26,27] By preventing and treating venous thromboembolisms (blood clots), heparin for anticoagulant therapy is associated with better prognoses in patients with certain tumors, such as breast cancer.[28]

Two types of heparins are widely used, unfractionated heparin (UFH) and low molecular weight heparin (LMWH). UFH is administered by injection and requires regular blood monitoring in the hospital setting. LMWH can be self-administered at home. The shortage of heparin examined in this analysis was associated with unfractionated heparin (heparin sodium) or injectable heparin, which for brevity we refer to as heparin throughout the rest of this analysis. We do not include LMWH heparin in the analysis. Although LMWH may be considered a first-line alternative, for this analysis, the alternatives for heparin were assumed to be other products approved as anticoagulants. The rationale for this choice was to assume that the alternative product would be available from within the same therapy class, not the drug class. There were two FDA-approved non-heparin anticoagulants considered substitutes for heparin—bivalirudin and lepirudin. Bivalirudin and lepirudin are both approved substitutes for heparin as an anticoagulant but are not efficacious for oncology-related uses.[29] Unlike the other two drugs in this study, asparaginase and nelarabine, which are solely used for the treatment of cancer, heparin has a much wider use other than as an anticoagulant during cancer treatment. Further, about 60 percent of the crude heparin used to manufacture heparin comes from China and is derived from pigs' intestines.[30] The shortage in the unfractionated heparin supply was traced to the African swine fever in China that eliminated between 25 percent to 35 percent of China's pig population since August 2018, resulting in a shortage of the necessary inputs.[30]

Data and Analytical Approach

The goal of this analysis is to examine trends in the utilization of the selected drugs used in the treatment of patients with cancer before, during, and after shortages, to examine whether there were differences in the unique number of patients taking the drug, the dosage associated with an administration, or the service charge.

This study was based on an analysis of IQVIA Medical Claims (Dx) for 2016-2020. The Dx data covered more than 205 million patients per year. They included pre-adjudicated claims generated by office-based physicians and specialists. The claims contained patient-level diagnoses, procedures performed, tests ordered, and drugs prescribed during visits to United States office-based healthcare professionals,

[26] Borsig, L., Wong, R., Feramisco, J., Nadeau, D. R., Varki, N. M., & Varki, A. (2001). Heparin and cancer revisited: mechanistic connections involving platelets, P-selectin, carcinoma mucins, and tumor metastasis. *Proceedings of the National Academy of Sciences*, *98*(6), 3352-3357.
[27] Lee, M. S., & Kong, J. (2015). Heparin: Physiology, Pharmacology, and Clinical Application. *Reviews in cardiovascular medicine*, *16*(3).
[28] Ma, S. N., Mao, Z. X., Wu, Y., Liang, M. X., Wang, D. D., Chen, X., ... & Tang, J. H. (2020). The anti-cancer properties of heparin and its derivatives: A review and prospect. *Cell Adhesion & Migration*, *14*(1), 118-128.
[29] Buck, M. L. (2015). Bivalirudin as an alternative to heparin for anticoagulation in infants and children. *The Journal of Pediatric Pharmacology and Therapeutics*, 20(6), 408-417.
[30] Vilanova, E., Tovar, A. M., & Mourão, P. A. (2019). Imminent risk of a global shortage of heparin caused by the African Swine Fever afflicting the Chinese pig herd. *Journal of Thrombosis and Haemostasis*, *17*(2), 254-256.

ambulatory and general healthcare sites, as well as hospitals and skilled nursing facilities. Dx data tracked the utilization of physician-administered medications, such as vaccines, biologics, and chemotherapy drugs. The data also tracked a patient's birth year, gender, and provider zip code. However, compared to the Surveillance, Epidemiology, and End Results (SEER), which is considered the authoritative source of cancer incidence and survival data in the United States, the IQVIA data may underestimate the population diagnosed with certain types of cancer and may not be representative of some demographic characteristics of the population with cancer, specifically in terms of race/ethnicity. A study that evaluated the representativeness and completeness of IQVIA compared to the SEER registry between 2006 and 2012 found that 67.6 percent and 13.0 percent of SEER cases had an active or inactive pharmacy claim, respectively, in IQVIA during the treatment assessment window for major cancers, such as breast and colon cancer.[31] This suggests that IQVIA data may capture more claims for people with breast cancer than those with color cancer. In addition, about 20 percent of the SEER records were not matched to IQVIA data, which indicates that IQVIA is capturing some claims that SEER is not. The study found that Blacks, Hispanics, and patients without insurance were less likely to be included in the IQVIA data. The study suggested that there may be differences in the types of patients included in IQVIA compared to SEER.

Inclusion and Exclusion Criteria

Our data extract included heparin, asparaginase, and nelarabine and their substitutes. Substitute drugs were identified by clinicians based on the sample of shortage cases and treatment alternatives that were either primarily pharmacy-dispensed or physician-dispensed. The underlying assumption was that the substitutes would be products in the same therapy class but not necessarily in the same drug class. The drugs that were selected for this analysis were all injectables that are primarily administered in a hospital or office-based setting, this means that the data only include unfractionated heparin.

In the IQVIA Dx database the drugs in shortage and their substitutes were identified using the Healthcare Common Procedure Coding System (HCPCS) codes listed in the procedure code field for each claim line item. Our analysis included two different forms of asparaginase (HPCPCS J9019 and J9020), both of which were considered shortage drugs. Compared to the number of patients with claims for asparaginase (J9019), the number of patients with claims for asparaginase "not otherwise specified" (J9020) was much lower. This may be because J9020 is not specified and thus providers rarely file a claim using this HCPCS code. Due to the dwindling numbers of patients receiving asparaginase (J9020), it was difficult to examine any trends in usage across months. Given the substantial difference in the strength of J9020, our analysis was limited to patients with claims for asparaginase (J9019) to ensure homogeneity in the patient-mix.[25] Exhibit 2 describes the list of medications and claims available in the IQVIA Dx dataset by HCPCS codes.

Exhibit 2: Description of shortage and substitute drugs and number of claims in Dx, 2016-2020

[31] Tran, Q., Warren, J. L., Barrett, M. J., Annett, D., Marth, M., Cress, R. D., ... & Cronin, K. A. (2020). An evaluation of the utility of big data to supplement cancer treatment information: linkage between IQVIA pharmacy database and the Surveillance, Epidemiology, and End Results Program. *JNCI Monographs*, *2020*(55),72-81.

Shortage Group	Generic Name	Shortage or Substitute	Route of Administration; Active Ingredient; Strength	HCPCS Code	Count of Claims
Asparaginase	Asparaginase	Shortage	Injection, asparaginase (Erwinaze), 1,000 iu	J9019	51,636
	Asparaginase	Shortage	Injection, asparaginase, not otherwise specified, 10,000 units	J9020	356
	Asparaginase	Shortage	Injection, asparaginase, recombinant, (Rylaze™), 0.1 mg	J9021	0
	Pegaspargase	Substitute	Injection, pegaspargase, per single dose vial	J9266	47,976
Nelarabine	Nelarabine	Shortage	Injection, nelarabine, 50 mg	J9261	24,392
	Fludarabine	Substitute	Injection, fludarabine phosphate, 50 mg	J9185	104,549
	Cladribine	Substitute	Injection, cladribine, 1 mg	J9065	39,480
	Clofarabine	Substitute	Injection, clofarabine, 1 mg	J9027	9,387
	Fludarabine phosphate	Substitute	Oral, Fludarabine phosphate, 10 mg	J8562	4
Heparin	Heparin	Shortage	Injection, heparin sodium, per 1000 units	J1644	129,814,496
	Heparin	Shortage	Injection, heparin sodium, (heparin lock flush), per 10 units	J1642	0
	Bivalirudin	Substitute	Injection, bivalirudin, 1 mg	J0583	861,972
	Lepirudin	Substitute	Injection, lepirudin, 50 mg	J1945	97
	Desirudin	Substitute	Unclassified drugs	J3490	0

Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Note: This exhibit includes the count of claims across all five years across all patients by HCPCS codes. It is not confined to cancer patients. No claims were identified for J9021 (Injection, asparaginase, recombinant, (Rylaze), 0.1 mg) as the effective date for the HCPCS code was outside of the study period. No claims were identified for J1642 (Injection, heparin sodium, (heparin lock flush), per 10 units) as it is mostly bundled with the procedure for which it is used such as anesthesia procedures. The injectable form of heparin substitute, Desirudin, is likely to be coded using HCPCS code J3490 (unspecified drugs) and therefore was not available in Dx. Four claims were found for nelarabine substitute fludarabine phosphate (J8562) as it is an oral drug and is less likely to be administered in the medical facility. Desirudin, Rylaze, heparin lock flush, and fludarabine phosphate were excluded from the analysis.

We identified claims with a cancer diagnosis using ICD-10-CM codes C00 through D49 (See Appendix 1). These ICD-10-CM codes represented diagnosis codes for cancers as defined by the SEER cancer registry and excluded the Z codes (which should be used only for a history of a condition), E codes (that denote hyperparathyroidism and other underlying conditions), and R codes (that describe the diagnostic signs related to cancers). In the Dx data, there was only one diagnosis code per line item, meaning that we could not identify primary versus secondary diagnoses, thus we retained all line items with a cancer diagnosis code for the analysis. Dx also listed the number of units associated with a service, and the service charge, but lacked details on how much the patient paid.[25] Appendix 2 shows the number of unique claims and patients across the five years of Dx data. We were unable to ascertain if the claims for the drugs of interest were used exclusively for the treatment of cancer (see Appendix 3).

Our final sample included 6,177 unique patients and 30,326 unique claims for asparaginase, 351,169 unique patients and 609,685 unique claims for heparin, and 8,876 unique patients and 55,223 unique claims for nelarabine (see Appendix 3). We excluded missing data and negative values for service charges as these were determined to be invalid fills (see Appendix 4). We also conducted a sensitivity analysis for heparin since it is used as an anticoagulant for a wide variety of conditions. As a sensitivity check, we performed our analyses using all claims for heparin to see if trends in the use of heparin for patients with cancer during the shortage period were different than general trends across all uses of heparin.

To identify the period of shortage, we used the dates of the shortage as published by FDA's Drug Shortage Database.[32] These dates represented the dates when FDA was notified or became aware of the shortage. This data included information that was self-reported by manufacturers about drugs in shortage, including the reason for the shortage, start date of the shortage, initial posting date of the shortage designation, date of updates to the shortage status, status of the shortage (current, resolved, discontinued), active pharmaceutical ingredient, therapeutic class, product form, and manufacturer name.

Shortage Period Analysis

We examined utilization during three phases of a shortage: before, during, and after a shortage, when possible. We also examined select demographic characteristics to understand whether there were differences across patient groups. Specifically, we calculated the average number of patients receiving a drug in a month by gender (male, female) and age categories (0-18, 19-39, 40-64, 65+) for each phase of the shortage.

Next, we examined trends in utilization, service charge,[33] and the number of patients receiving a drug before, during, and after a shortage. The total service charge included all charges submitted in a given claim and HCPCS code. We calculated the average service charge, which was defined as the total service charge divided by the count of drugs provided in a given claim and HCPCS code. We used the average service charge as a proxy for the price patients may pay.

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[32] U.S. Food and Drug Administration. Drug Shortages Database.
https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm

[33] "Service charge is our proxy measure for cost. Generally, a charge is the dollar amount a health care provider sets for services rendered before negotiating any discounts; the charge can be different from the amount paid. To patients, costs usually represent the amount they have to pay out-of-pocket for health care services. IQVIA defines "service charge" as the charges related to a medical service. In this analysis, "service charges" are standardized to be total service charge divided by the count of drugs.

Chapter 2. Results

In this chapter, we explored potential demographic differences in the receipt of shortage drugs. We examined the age and gender distribution of patients during three phases – pre-shortage, shortage, and post-shortage, where applicable– for each drug of interest. Specifically, for asparaginase and heparin, the shortage did not resolve in the period of analysis and as such there is no "post-shortage" period. Next, we explore trends in the number of patients receiving shortage drugs and their substitutes.

Age and Gender Distribution of Patients Receiving Shortage Drugs During Pre-Shortage, Shortage, and Post-Shortage Periods

Exhibit 3 shows that the majority of patients using asparaginase and nelarabine were male and 18 years or younger, while most users of heparin were females and patients 40 years or older. As shown in Exhibit 3, for all three shortage drugs, albeit small, the relative proportion of female patients taking the drug declined during the shortage periods compared to pre-shortage periods with a corresponding increase in the proportion of male patients. It is possible that female patients differed in some ways, e.g., the underlying conditions or comorbidities, compared to male patients; however, given the available data, we were unable to examine this further. Across all three drugs of interest, there was no clear pattern of an increase or decrease in the proportion of patients across all age groups.

Exhibit 3: Patient Characteristics by Shortage Period and Drug

	Pre-Shortage		Shortage		Post-Shortage		2016-2020	
	Number of Patients per Month	Proportion of Patients[1]	Number of Patients per Month	Proportion of Patients[1]	Number of Patients per Month	Proportion of Patients[1]	Average Number Patients per Month	Proportion of Patients[1]
Asparaginase								
All	67	100%	56	100%	n/a[2]	n/a[2]	57	100%
Sex								
Male	39	59%	35	63%	n/a[2]	n/a[2]	35	62%
Female	28	41%	21	37%	n/a[2]	n/a[2]	22	38%
Patient Age Categories								
0-18 years	54	80%	46	82%	n/a[2]	n/a[2]	47	82%
19-39 years	11	16%	9	15%	n/a[2]	n/a[2]	9	16%
40+ years	3	4%	1	2%	n/a[2]	n/a[2]	1	2%
Nelarabine								

	Pre-Shortage		Shortage		Post-Shortage		2016-2020	
	Number of Patients per Month	Proportion of Patients[1]	Number of Patients per Month	Proportion of Patients[1]	Number of Patients per Month	Proportion of Patients[1]	Average Number Patients per Month	Proportion of Patients[1]
All	15	100%	45	100%	58	100%	31	100%
Sex								
Male	11	73%	34	77%	43	75%	23	75%
Female	4	27%	10	23%	15	25%	8	25%
Patient Age Categories								
0-18 years	6	40%	34	75%	42	73%	20	65%
19-39 years	5	32%	8	17%	14	24%	7	23%
40+ years	4	28%	4	8%	2	4%	4	12%
Heparin								
All	8,304	100%	7,371	100%	n/a	n/a	7,713	100%
Sex								
Male	2,702	33%	2,679	36%	n/a	n/a	2,688	35%
Female	5,602	67%	4,692	64%	n/a	n/a	5,025	65%
Patient Age Categories								
0-18 years	138	2%	82	1%	n/a	n/a	103	1%
19-39 years	610	7%	514	7%	n/a	n/a	549	7%
40+ years	7,554	91%	6,774	92%	n/a	n/a	7,060	92%

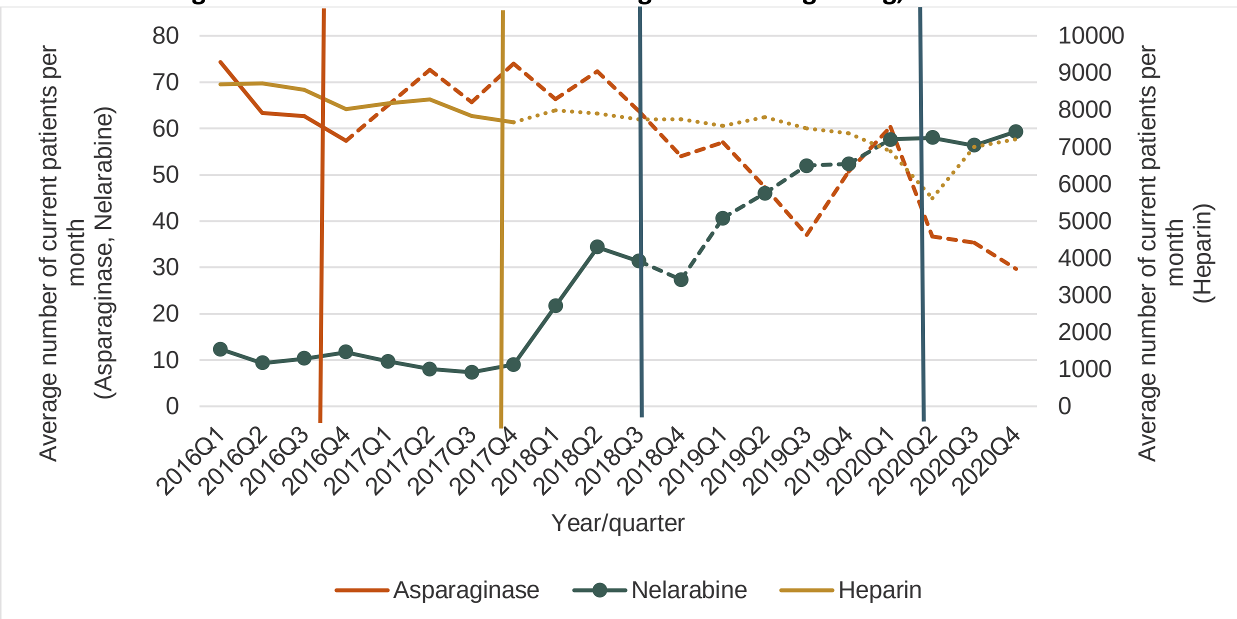
Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.

Note: 1. The "proportions of patients" columns indicate average, unique, current patients within that period. 1. n/a denotes that the shortage was not resolved. As of March 2024, heparin was still in shortage since November 2017. The shortage period for asparaginase was from October 2016 to August 2021. The shortage period for nelarabine was from October 2018 to January 2020.

Number of New Patients and Current Patients for Shortage Drugs

To further understand how drug shortages influenced the number of patients being administered these three drugs, we examined the quarterly change in the number of patients receiving each shortage drug per month (Exhibit 4).

Exhibit 4: Average Number of Current Patients Taking Each Shortage Drug, 2016-2020



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Note: The dotted lines represent shortage periods for each drug. As of March 2024, heparin was still in shortage since November 2017. The shortage period for asparaginase was from October 2016 to August 2021. The shortage period for nelarabine was from October 2018 to January 2020.

For asparaginase, despite temporary upticks, the average number of patients receiving the drug per month exhibited an overall decline since the drug was listed in shortage. Appendix 6 shows the number of new patients (unique patients that have a first claim for a given drug in each month) during the same period, which follows a similar pattern of temporary upticks with an overall decline. However, it is important to note that this decrease coincided with the early phase of the COVID-19 public health emergency, which may have further contributed to the decline in overall patients as well as new ones. During the COVID-19 pandemic, especially in the early phase, health care institutions implemented several treatment prioritization strategies for chemotherapy, such as reduction in treatments, treatment breaks, and oral medications, so it is possible that reduced access to health care institutions also contributed to the decline.[34]

In contrast to asparaginase, the number of patients using nelarabine began to increase in Q1 2018, three quarters before the drug was listed in shortage, followed by a decline at the beginning of the shortage period, Q3 2018 and Q4 2018, and a continued increase after. Because manufacturers notify FDA about a potential shortage before the drug is listed on the FDA shortage database, it is possible that the early uptick illustrates a lag in the notification time. Further, this early uptick may also be capturing an increase

[34] Chow, M. C., Chambers, P., Singleton, G., Patel, J., Cooper, S., Mythen, C., ... & Vindrola-Padros, C. (2021). Global changes to the chemotherapy service during the covid-19 pandemic. *Journal of Oncology Pharmacy Practice*, *27*(5), 1073-1079.

in nelarabine demand after a 2018 study demonstrated the effectiveness of the drug against T-cell acute lymphoblastic leukemia.[35] As a result, demand for the drug appears to have been sustained despite the shortage. Appendix 7 shows that the number of new users followed a steady increase during the shortage period, which suggests that there was new demand for the drug.

For heparin, there was little change in the number of patients using the drug when the shortage period started; a gradual decline began in 2020 which coincided with the onset of the COVID-19 pandemic. However, this downward trend seemed to have reversed by Q3 of 2020. The number of new users follows a similar pattern across the shortage period (Appendix 8). This may be because during the pandemic patients being treated for cancer were prioritized for treatment relative to patients with other conditions.

Number of Current Patients for Shortage Drugs and Their Substitutes

To investigate the use of substitute drugs during shortages, we examined the number of patients taking each shortage and substitute drug per month during the pre-shortage, shortage, and post-shortage periods (Exhibit 5).

Exhibit 5: Monthly Number of Patients Taking Shortage and Substitute Drugs

Shortage Group	Drug Name	Shortage or Substitute	Pre-shortage	Shortage	Post-shortage
Asparaginase	Asparaginase	Shortage	67	56	n/a
	Pegaspargase	Substitute	250	217*	n/a
Nelarabine	Nelarabine	Shortage	15	45*	58*#
	Cladribine	Substitute	62	56*	50
	Clofarabine	Substitute	13	4*#	6*
	Fludarabine	Substitute	300	162*	92*#
Heparin	Heparin	Shortage	8,305	7,371*	n/a
	Bivalirudin	Substitute	17	12*	n/a
	Lepirudin	Substitute	1	2	n/a

Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.

Note: T-tests were conducted between the pre-shortage and shortage period for all shortage groups and between the shortage and post-shortage period for nelarabine only. P <0.05 are considered statistically significant and are denoted by a "*"."#" denotes t-tests of unequal variance as per the F test. Due to few numbers of current users for Lepirudin, we were not able to perform F test to check variance and the T test was conducted assuming equal variance. n/a denotes "not applicable" as the shortage had not yet been resolved during the period of analysis.

As previously mentioned, asparaginase and pegaspargase are both chemotherapy drugs used to treat children with ALL. The average number of current patients per month for pegaspargase was consistently greater than that of its parent drug, asparaginase, which could be due to the lower cost for pegaspargase (to be discussed in more detail later). Additionally, 60 percent of patients face severe allergies and toxicity

[35] Dunsmore, K. P., Winter, S., Devidas, M., Wood, B. L., Esiashvili, N., Eisenberg, N., ... & Hunger, S. (2018). COG AALL0434: A randomized trial testing nelarabine in newly diagnosed t-cell malignancy.

with pegaspargase, and pegaspargase has a longer half-life (the time it takes for a drug's active substance in the body to reduce by half) than asparaginase.[36] Together, this means that although it may be less expensive, for many patients, pegaspargase may not be an appropriate substitute for asparaginase. Further, we note there was a global lack of supply of the source for both these drugs – *E. chrysanthemi* (Erwinaze) – which may mean that pegaspargase was not necessarily more available than asparaginase during the shortage period.[37,38] These factors suggest that asparaginase patients may not have been able to substitute with pegaspargase during the shortage period and may explain the observed decline in the number of patients for both asparaginase and pegaspargase. (This is graphically depicted in Appendix Exhibit 9.)

For nelarabine, the average number of current patients significantly increased from 15 patients in the pre-shortage period to 45 patients (200 percent increase) in the shortage period and continued to increase in the post-shortage period to 58 patients (29 percent increase compared to the shortage period). The increase in demand began prior to the shortage, likely due to the promising research findings regarding efficacy of nelarabine for an expanded population of patients.[39] The promising research findings[40] for nelarabine likely did not apply to its three substitutes, all of which showed a persistent and significant decline in the number of current patients receiving the drugs from the pre-shortage to the shortage and post-shortage periods. (This is graphically depicted in Appendix Exhibit 10.)

For the third drug, heparin, the average number of patients with cancer using heparin declined from 8,305 in the pre-shortage period to 7,371 (13 percent reduction) in the shortage period with a slight decline in the number of patients using bivalirudin and lepirudin combined, albeit small sample sizes warrant caution on interpreting these as actual declines. The high cost of bivalirudin and lepirudin compared to heparin likely impacted usage of these substitutes – the use of both substitutes is much lower than that of heparin and there is no evidence of substitution of these drugs for heparin during the shortage period. We note, however, that these substitutes do not include LMWH which has increasingly been used as a substitute for UFH and which can cost less than UFH.[41] At the time the substitutes were identified for this analysis, LMWH had not been widely used as a substitute for UFH, and substitutes were assumed to include drugs within the same therapy class but not necessarily in the same drug class. (This is graphically depicted in Appendix Exhibit 11.)

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[36] Verma, A., Chen, K., Bender, C., Gorney, N., Leonard, W., & Barnette, P. (2019). PEGylated E. coli asparaginase desensitization: an effective and feasible option for pediatric patients with acute lymphoblastic leukemia who have developed hypersensitivity to pegaspargase in the absence of asparaginase Erwinia chrysanthemi availability. *Pediatric Hematology and Oncology*, *36*(5), 277-286.
[37] Jensen L, Wheeler M. Asparaginase Erwinia Chrysanthemi.; Drug Shortages. October 11, 2018, https://www.drugs.com/drug-shortages/asparaginase-erwinia-chrysanthemi-482; last accessed August 23, 2022.
[38] Medawar, C. V., Mosegui, G. B. G., Vianna, C. M. D. M., & Costa, T. M. A. D. (2020). PEG-asparaginase and native Escherichia coli L-asparaginase in acute lymphoblastic leukemia in children and adolescents: a systematic review. *Hematology, transfusion and cell therapy*, *42*, 54-61.
[39] Personal consultation with Jeffrey Lombardo, PharmD. (2022).
[40] Dunsmore, K. P., Winter, S., Devidas, M., Wood, B. L., Esiashvili, N., Eisenberg, N., ... & Hunger, S. (2018). COG AALL0434: A randomized trial testing nelarabine in newly diagnosed t-cell malignancy.
[41] Angels for Change. (2018). Angels for Change announces 10 drugs added to Project Protect. Accessed September 26, 2022. https://www.angelsforchange.org/news-updates/angels-for-change-announces-10-drugs-added-to-project-protect

The number of patients with a cancer diagnosis represented 9 percent of all heparin users in the sample (more details can be found in Appendix 3). To examine the robustness of our findings, we conducted the same descriptive analysis including all heparin users in the sample. Our findings showed a modest increase in all heparin users and a decrease in bivaliridudin users. During the COVID-19 pandemic, heparin had been shown to have a positive impact on the treatment of COVID-19 patients due to its anticoagulant function.[42] The results suggest that the increase in users is driven by non-cancer patients. Throughout the rest of this analysis, unless otherwise specified, we focus our analysis using the sample of cancer patients only.

Exhibit 6: Monthly Patients for Heparin and its substitutes Among All Claims

Drug Name	Average pre-shortage	Average shortage
Heparin	106,712	107,327*
Bivalirudin	3,777	2,458*
Lepirudin	1	1*

Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Note: *Indicates values of p<0.05 in t-tests between compared groups as determined from F test.

Number of Units and Service Charge per Patient for Shortage Drugs and Their Substitutes

To test the hypothesis that drug shortages may result in a decline in units available for patients and an increase in the service charge, as demand outpaces supply, we explored trends over time for the shortage drugs.

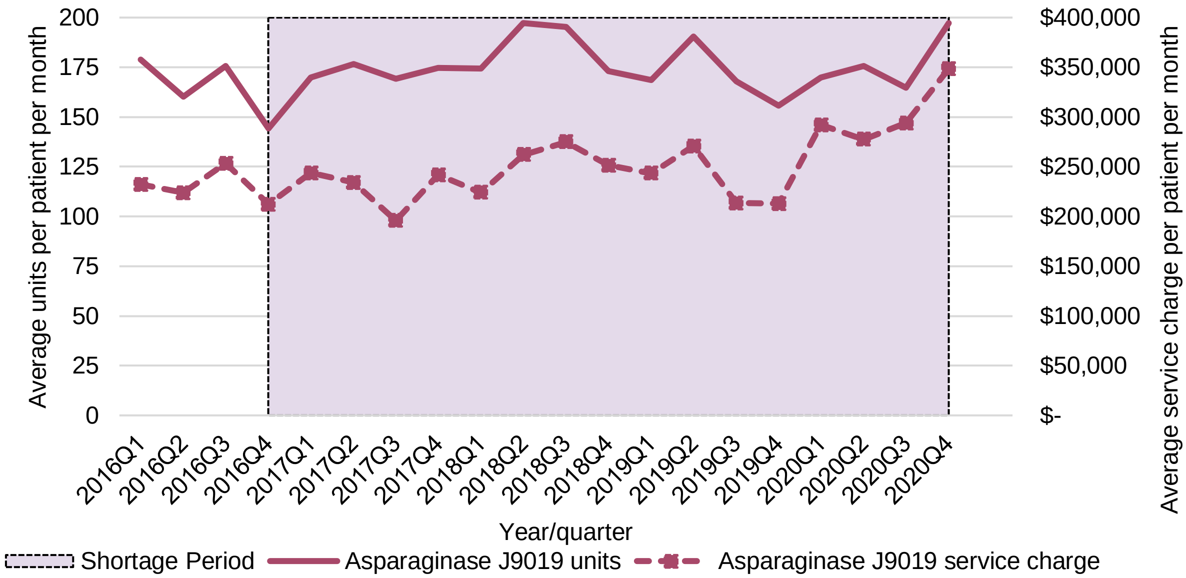
Exhibit 7 depicts the trend in units sold and service charges for asparaginase. During the shortage period, the average number of units given to a patient per month initially increased from 144 units in Q4 2016 to 197 units (37 percent increase) in Q2 2018. Then, units sold decreased until Q4 2019 and finally began to trend upwards in 2020. In other words, we did not find evidence of decreased utilization during the period of analysis. This suggests that the market was able to supply more of the drug in shortage. The average units sold per patient for asparaginase's substitute, pegaspargase, remained low and steady during the entire data period except for Q3 2019 (see Appendix 12).

Next, we examined the price per drug, measured using the service charge variable. We note that the average service charge per patient per month varied widely for the selected drugs. Specifically, the average price for asparaginase, nelarabine and heparin in Q1 2016 was $232,285, $78,097, and $83, respectively. The average unit service charge per patient for asparaginase increased starting mid-way through the shortage period (Q2 2018) compared to the pre-shortage period, but then dropped below the pre-shortage period in Q3 and Q4 2019. Finally, the average service charge increased in the shortage period, reaching a high of $348,524 per unit in Q4 2020. On net, there was a small increase in the price of asparaginase after the shortage began. This rise in cost could be due to the increased use, during the

[42] Kopp, R. The Role of Heparin in COVID-19: An Update after Two Years of pandemics. J Clin Med 2022, 11(11): 3099.

shortage, of *E. chrysanthemi* asparaginase over *Escherichia Coli* asparaginase. *Escherichia Coli* asparaginase causes more allergic reactions than *E. chrysanthemi* asparaginase, which could explain the higher demand for the costlier *E. chrysanthemi* asparaginase.[43]

Exhibit 7: Average Units and Service Charges Per Patient Per Month for Asparaginase

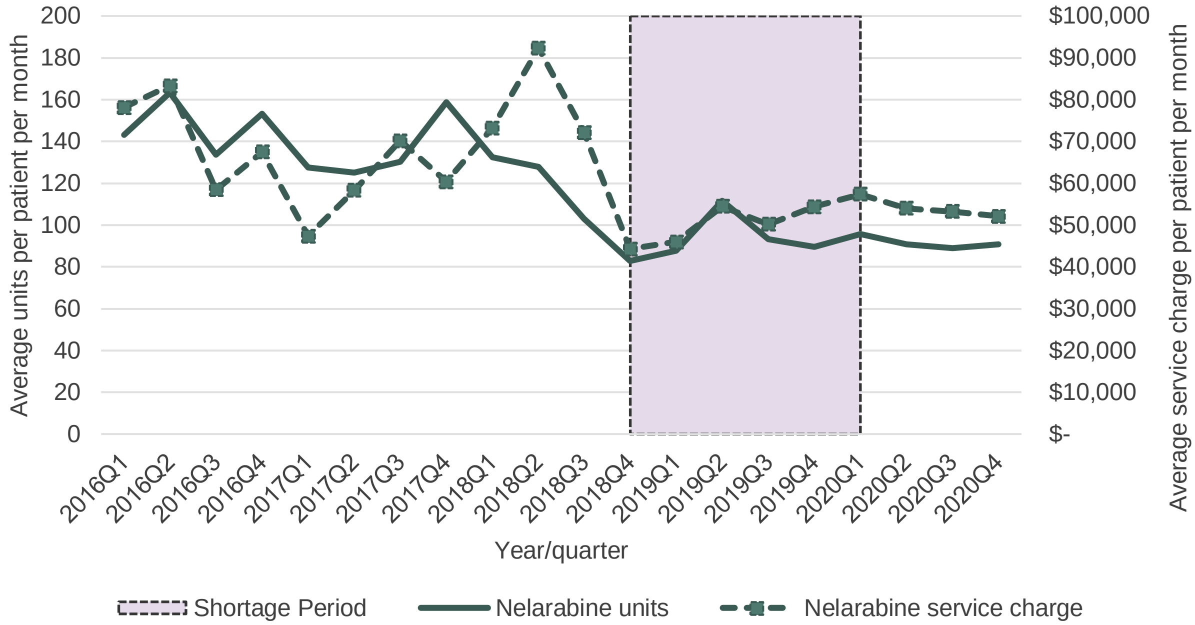


Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Note: Shortage period for asparaginase was from October 2016 to March 2020. Asparaginase (J9019) is an injection, asparaginase (Erwinaze®) of 1,000 units.

Exhibit 8 illustrates trends for nelarabine. Exhibit 8 shows that utilization fell shortly before and during the shortage and that utilization remained lower than baseline after the shortage was resolved. During the shortage period, the average units per patient per month ranged from 83 to 96 units compared to a range of 103 to 159 units in the pre-shortage period. Average units per patient for its substitute, clofarabine, fluctuated between 97 and 191 units compared to the pre-shortage period (range of 113 and 188 units) (Appendix 13). For another substitute, fludarabine, the average units per patient remained steady across the periods of interest except for a brief increase in 2020 (Appendix 13). In addition, the per patient service charges were lower for nelarabine during the shortage compared to the pre-shortage period.

[43] Kloos, R. Q., van Litsenburg, R. R., Wolf, S., Wismans, L., Kaspers, G. J., Uyl-de Groot, C. A., ... & van der Sluis, I. M. (2019). A cost-effectiveness analysis of Erwinia asparaginase therapy in children with acute lymphoblastic leukemia. *Pediatric blood & cancer*, *66*(1), e27458.

Exhibit 8: Average Units and Service Charges Per Patient Per Month for Nelarabine

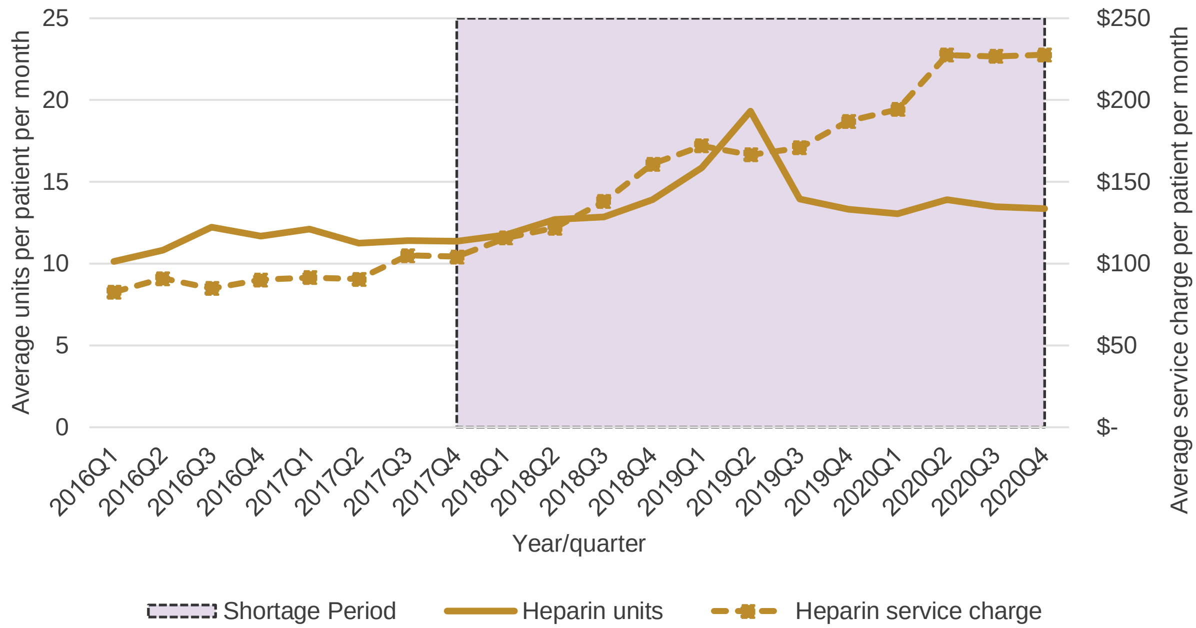


Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Note: Shortage period for nelarabine was from October 2018 to January 2020

Exhibit 9 displays results for heparin for the sample of patients with cancer and shows that utilization trended upward until mid-2019. Exhibit 9 also shows that the per patient service charge for heparin increased steadily from the pre-shortage period through the shortage period examined. During the heparin shortage, the average units per patient for its substitute, bivalirudin, increased between Q4 2017 and Q2 2019 (Appendix 14). However, due to the small number of patients (fewer than 25 in any month) using bivalirudin, this change should be interpreted with caution. Due to the extremely low number of patients (fewer than 5 in any month) using lepirudin, the changes in units per patient are not discussed.

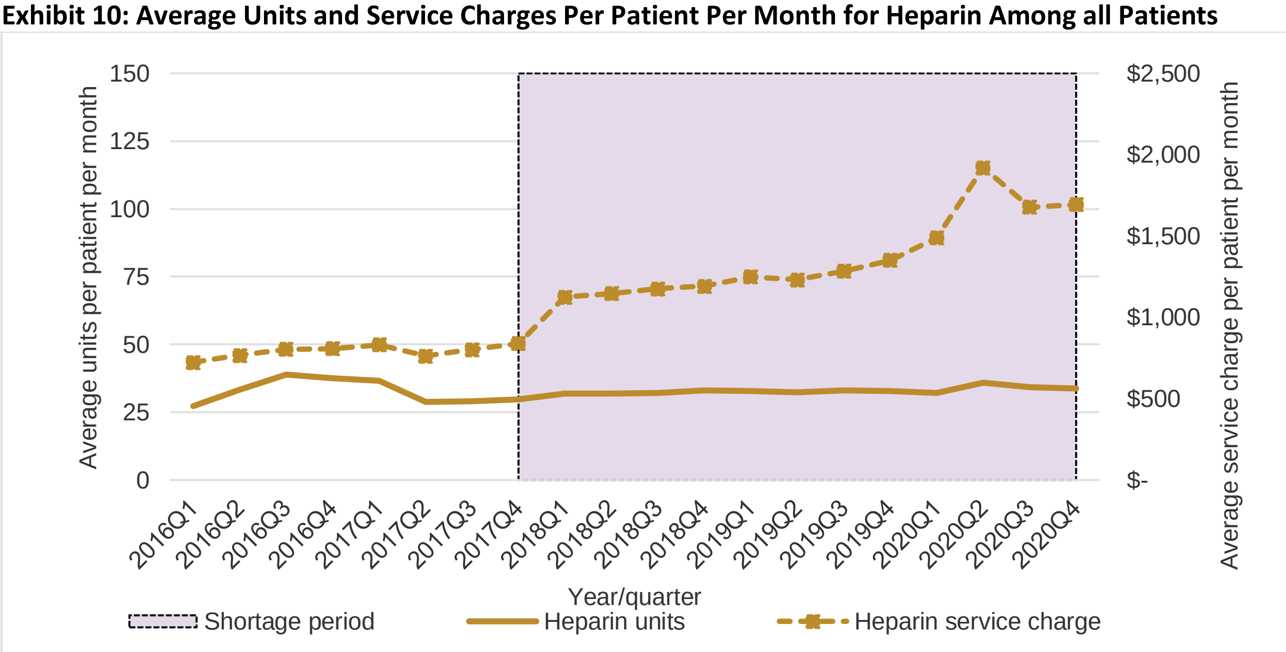
Because heparin is most used for conditions other than cancer, we also explored trends in use and service charges for all indications. Exhibit 10 shows the average units and service charges per patient per month among all patients for which a claim for heparin was submitted. The units per patient in the pre-shortage period ranged between 27 to 39 units compared to a range of 30 to 36 units during the shortage period examined. Like what was observed among cancer claims, the service charge per patient for all claims increased during the shortage period from $840 in Q4 2017 to $1,921 in Q2 2020. Although the service charge declined by Q4 2020, it was still at least double that of the service change in the pre-shortage period.

Exhibit 9: Average Units and Service Charges Per Patient Per Month for Heparin Among Patients with Cancer



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Note: As of March 2024, heparin was still in shortage since November 2017.

Exhibit 10: Average Units and Service Charges Per Patient Per Month for Heparin Among all Patients



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Note: As of March 2024, heparin was still in shortage since November 2017.

Number of Patients Switching to Substitute Drugs

In addition to analyzing the number of patients receiving each shortage drug and its substitutes, we also investigated the number of patients switching from the shortage drug to the substitute drugs per month. Appendix 15 demonstrates that, on average, fewer than five patients switched from asparaginase to pegaspargase per month during the shortage period. Appendix 16 shows that there were no patients that switched from nelarabine to clofarabine or to cladribine during the pre-shortage, shortage, or post-shortage periods, and that two patients or fewer per month switched from nelarabine to fludarabine in each quarter during the shortage period. Only one patient switched during the entire pre-shortage period from nelarabine to fludarabine. The results displayed in Appendix 17 suggest that, on average, two or fewer patients switched from heparin to bivalirudin during the pre-shortage and shortage periods and no patients switched post-shortage. In addition, no patients switched from heparin to lepirudin during the pre-shortage period and only one patient on average per month switched during the post shortage period. This analysis, however, did not include LMWHs, which can be substitutes for unfractionated heparin and as such, we cannot conclude that substitution did not occur. Overall, our analysis indicates there may be little substitution when a drug goes in shortage. This finding points to anecdotal evidence that when the drug of choice is in shortage, there are factors that make the use of alternative drugs challenging for affected users (e.g., differences in the formulation, dosage, or form).

Chapter 3. Discussion and Conclusion

We examined two oncology drugs and one drug used in the regimen of patients with cancer to understand whether there were changes in service charges or utilization during the pre-shortage, shortage, or post shortage periods, where applicable. Based on our analysis, when these drugs were in shortage between 2016 and 2020, there was a decline in the number of patients using asparaginase and heparin (shortages that were due to supply disruptions), and an associated increase in the number of patients using nelarabine (shortage due to an increase in demand). However, the associated changes in the number of patients did not coincide with the observed trend in the administration of the drugs. For example, a decrease in the number of patients using asparaginase was associated with an increase in the service charge and units administered, and an increase in the number of patients using nelarabine was associated with a decrease in the service charge and units administered. Further, our analysis demonstrated that declines in the administration of a shortage drug did not coincide with an increase in usage of our identified substitute drugs. Notably, the average service charge of heparin and asparaginase did increase during its shortage period, while the service chargers decreased for nelarabine. These results point to the complexity of the issues underlying the resolution of shortages and their impacts. Generally, minimizing the impact of shortages requires resolving a shortage quickly, which involves increasing supply to meet demand. However, increasing supply depends on the ability of manufacturers and providers to increase capacity and access quickly, as well as the ability for patients to switch to alternative products. Further, the ability for patients to switch to alternative products is influenced by many factors including, the number of alternatives available, comorbidity profile, cost, insurance coverage, or sociodemographic characteristics such as age.

Factors contributing to the specific reason for each drug shortage and the suitability of substitutes appeared to be associated with the timing, direction, and magnitude of changes in the usage of shortage drugs. For instance, the lack of substitution of pegaspargase for asparaginase was likely due to the limited supply of the common raw ingredient for both drugs, potential adverse reactions for some patients to the substitute drug, and high cost. In addition, the shortage of asparaginase was not resolved until August 2021, which involved FDA working with available manufacturers to increase supply.[44] This increase in supply from other manufacturers may explain the increase in the number of units of asparaginase during the shortage period. For nelarabine, findings from a clinical trial that concluded in 2018 led to an increase in demand and gaps in supply that continued months after the shortage was reported resolved and where we did not observe substitution to alternative products. Finally, heparin was in high demand due to its use for other conditions during the COVID-19 pandemic and worldwide supply was curtailed as a result of the African swine flu in China in 2018. Heparin's substitutes were also expensive and associated with adverse side effects, and they tended to be used less frequently than heparin. While the shortage of heparin is ongoing as of March 2024, the provider community has utilized several conservation strategies, including drug rationing, therapeutic substitution, and compounding of needed products using the limited

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[44] Angels for Change. (2018). Angels for Change announces 10 drugs added to Project Protect. Accessed September 26, 2022. https://www.angelsforchange.org/news-updates/angels-for-change-announces-10-drugs-added-to-project-protect

available stock.[45] However, these efforts were not captured in our data because they are decisions made at the hospital or health system level, not directly linked to the prescriber behavior. For example, compounded drugs have different safety and reimbursement requirements, including prior authorizations, or authorizations that are not tracked electronically so they would not appear in IQVIA.

Another factor that is important to consider is the number of manufacturers or products within a drug class that are available when a product goes into shortage. In the case of heparin, there were 421 active NDCs, and not all of them were associated with the manufacturer of the drug in shortage. This means that one product formulation for unfractionated heparin might be in shortage while another manufacturer for a similar unfractionated heparin product might have an adequate supply in the same month. In such instances, patients may shift from one NDC to the other, but since our grouping is at the active ingredient level, the substitution may not be directly observable. This means that we would not be able to observe a change in the distribution of use among NDCs if the number of users remained constant overall, but changes in price may indirectly demonstrate that there has been a shift in the use patterns for heparin amongst its many NDCs as a result of the shortage.

Each drug shortage is unique and its impact on patient care is driven by the specific nature of the drugs, its manufacturing context, the patients who use the drugs, and other market forces. As such, drug shortages have varying effects on patients. For example, we observed differences in the demographic profile (i.e., sex and age) across the drugs examined. Further research should examine patient specific trends in cost and utilization trends for drugs in shortage to understand how individual factors, such as race and ethnicity, age, sex, and healthcare system infrastructure, can impact access to drugs.

Taken together, understanding the impacts of shortages on patients, as measured by changes in the number of patients, utilization, and costs, for these three drugs presents only a subset of the overall impacts. Further research is needed to understand how the results from this study apply to other shortages more generally.

Limitations

This study has several limitations. A primary limitation is that this report focused on a select group of patients with cancer who received the drugs of interest and not on the patients who needed these drugs but were unable to access them due to shortages. This limits the interpretations of our results. In addition, our main analysis was a cross-sectional analysis of patients receiving shortage drugs at different time points rather than a longitudinal analysis of the same patients over time. Therefore, we were unable to observe changes in access to and usage of medications at the patient level and explore whether treatment trajectories differed by patient characteristics.

Additionally, there are limitations to the IQVIA Dx data. First, it captured pre-adjudicated claims, and therefore the service charge represented what a physician charged but was not indicative of the final amount paid by plans according to the negotiated reimbursement rates for each service and drug. The

[45] Benge, C. D., & Burka, A. T. (2019). Heparin drug shortage conservation strategies. *Federal Practitioner*, *36*(10), 449.

negotiated rate is generally lower than the service charge and can differ by insurance plan, so we are missing some heterogeneity in our charge estimates. Also, the service charge can be overestimated because specific claim line items or charges may be denied. For the drug components, our data capture only list prices, not the actual amounts paid; however, rebates and other discounts are less frequent for infusion drugs that were examined in this study, compared to retail drugs. Furthermore, the patient cost sharing component is not reflected, and this is often an important determinant of access to drugs.[46][47] Second, we found issues with missing data, negative values for service charges, and the inclusion of only four diagnoses codes compared to the 12 codes typically found in claims.

To identify the period of shortage, we used the dates and reasons for the shortage as published by FDA. These dates represent the dates when FDA was notified or became aware of the shortage and may not be when the shortage occurred. The FDA Drug Shortages Database is self-reported by manufacturers and is missing significant information for fields that are considered optional. FDA uses the self-reported information submitted as a starting point to assess the nature of the shortage and its underlying cause. For example, it is possible for a manufacturer to select "Other" or "Unknown" as the cause of the shortage when they initially submit their notification to FDA, and then FDA may learn during its assessment that the underlying cause is a manufacturing quality issue. In this case, the public database will provide the information initially provided to FDA ("Other" or "Unknown"). Another limitation of the data is that a manufacturer may not report the shortage of a drug to FDA until clinicians or other stakeholders report it. In such case, and as was observed in some of our analyses, there may be a decrease in the utilization of a drug before FDA's officially determinates that the drug is in shortage. This may explain why we observe minimal responses in terms of use at the onset of a shortage. The other issue is our analysis defined a shortage at the active ingredient level. The advantage of this approach is that it captures a broader range of products that may also be affected by the shortages, such as immediate substitutes (i.e., different dosage, strengths, and forms may be used as a substitute in rare occasions when that form does not also go into shortage). The disadvantage of this approach is that we cannot identify important characteristics about the products involved in shortages, and that there may be variation in price changes and duration depending on strength, form, and dose differences.

Conclusion

Our analysis did not reveal conclusive evidence regarding the use and price of three drugs that are indicated for cancer care and that entered shortage status in 2016-2020. We also observed disparate results in the use of substitute drugs. Use of the drug in shortage and its substitutes appears to depend

[46] BettareLLi MM. Cost sharing: implications of a well-intended benefits strategy. J Manag Care Spec Pharm. 2022 Feb;28(2):275-277. doi: 10.18553/jmcp.2022.28.2.275. PMID: 35098750; PMCID: PMC10372964.

[47] Ismail WW, Witry MJ, Urmie JM. The association between cost sharing, prior authorization, and specialty drug utilization: A systematic review. J Manag Care Spec Pharm. 2023 May;29(5):449-463. doi: 10.18553/jmcp.2023.29.5.449. PMID: 37121255; PMCID: PMC10388011.

not just on the reason of the shortage (increase in demand vs manufacturing delay), but also on the number of manufacturers and substitutes available, and the effectiveness and safety profile of the alternative drug relative to the drug in shortage. The analysis also showed that the duration of these shortages can be long-lasting, with some shortages lasting almost five years. The results suggest that larger studies that include more drugs and more data are needed to better understand the underlying dynamics and characteristics of shortages and their impacts. While the analysis in this study allowed us to observe changes in the number of patients, service charges, and supplied units across the pre-shortage, shortage, and post-shortage periods, the study data did not allow us to estimate the number of patients that were unable to access these drugs due to the shortages. Future analysis can also explore cohorts of patients longitudinally to determine whether the use of shortage drugs or their substitutes differ by sociodemographic, geographical, clinical, and health insurance characteristics. Longitudinal studies could also determine an appropriate period of time to follow patients with specific diagnosis codes irrespective of their use of the shortage or substitute drugs to estimate the impacts of not receiving the shortage drug or switching to a substitute.

Appendix

Appendix Exhibit 1: ICD- 10- CM Codes for Cancer

ICD- 10 CM Codes for Cancer	Description of Neoplasms
C30-C39	Malignant neoplasms of respiratory and intrathoracic organs
C40-C41	Malignant neoplasms of bone and articular cartilage
C43-C44	Melanoma and other malignant neoplasms of the skin
C45-C49	Malignant neoplasms of mesothelial and soft tissue
C50-C50	Malignant neoplasms of breast
C51-C58	Malignant neoplasms of female genital organs
C60-C63	Malignant neoplasms of male genital organs
C64-C68	Malignant neoplasms of urinary tract
C69-C72	Malignant neoplasms of the eye, brain, and other parts of the central nervous system
C73-C75	Malignant neoplasms of thyroid and other endocrine glands
C76-C80	Malignant neoplasms of ill-defined, other secondary and unspecified sites
C7A-C7A	Malignant neuroendocrine tumors
C7B-C7B	Secondary neuroendocrine tumors

ICD- 10 CM Codes for Cancer	Description of Neoplasms
C81-C96	Malignant neoplasms of lymphoid, hematopoietic, and related tissue
D00-D09	In situ neoplasms
D10-D36	Benign neoplasms, except benign neuroendocrine tumors
D37-D48	Neoplasms of uncertain behavior, polycythemia vera, and myelodysplastic syndromes
D3A-D3A	Benign neuroendocrine tumors
D49-D49	Neoplasms of unspecified behavior

Source: https://training.seer.cancer.gov/icd10cm/appendix-a/

Appendix Exhibit 2: Unique Claims and Patients in IQVIA Dx file for Shortage and Substitute Drugs

Shortage group	Drug name	Dx (2016-2020)	
		Number of unique claims	Number of unique patients
Asparaginase	Asparaginase	20,608	1,175
	Pegaspargase	17,572	5,783
Heparin	Bivalirudin	225,998	158,992
	Heparin	35,475,142	3,880,926
	Lepirudin	37	25
Nelarabine	Cladribine	17,748	2,582
	Clofarabine	3,581	231
	Fludarabine	44,379	5,825
	Nelarabine	9,272	657

Source: Authors' analysis of 2016 – 2020 IQVIA Dx data
Note: Dx data are Pre-adjudicated Open-Source Medical Professional and Institutional Claims (IQVIA).

Appendix Exhibit 3: Claims and Patients by Drug (Total and with cancer)

Drug Group	Full Dataset		Patients With Cancer	
	Unique claims	Unique patients	Unique Claims	Unique Patients
Asparaginase	31,439	6,305	30,326	6,177
Heparin	9,126,630	3,930,198	609,685	351,169
Nelarabine	57,958	9,253	55,223	8,876
Total	9,216,027	3,945,756	695,234	357,346

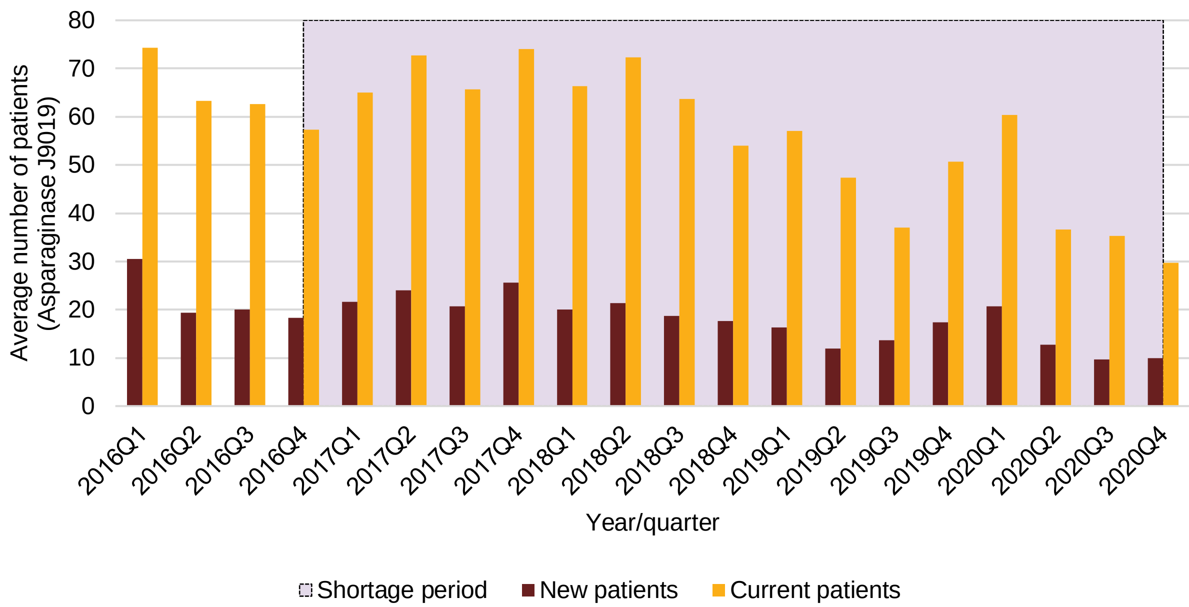
Source: Authors' analysis of 2016 – 2020 IQVIA Dx data
Note: This table includes shortage and substitute drugs identified using HCPCS codes listed in Exhibit 2

Appendix Exhibit 4: Claims and Patients with Zero or Negative Units of Service Among Patients with A Cancer Diagnosis

Shortage Group	Distinct Claims with Zero or Negative Service Units	Distinct patients With Zero or Negative Service Units
Asparaginase	31	12
Heparin	36	18
Nelarabine	16	6
Total	83	36

Source: Authors' analysis of 2016 – 2020 IQVIA Dx data

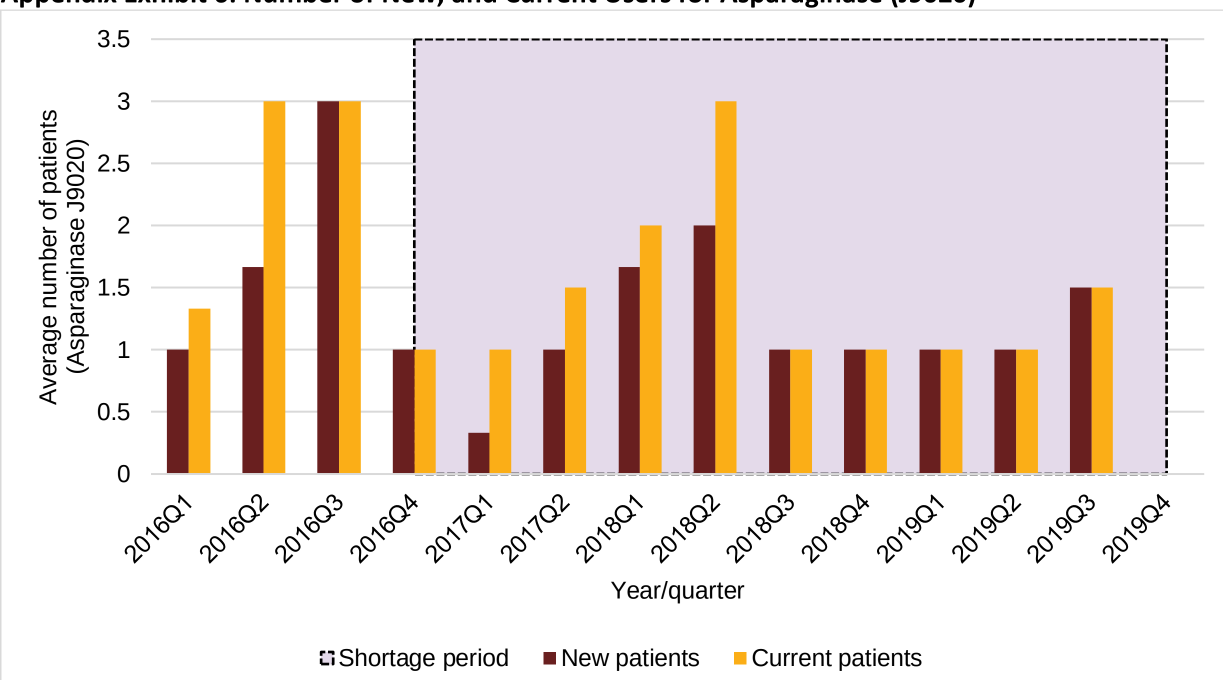
Appendix Exhibit 5: Number of New, and Current Users for Asparaginase (J9019)



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.

Note: Shortage period for asparaginase started in October 2016; shortage ended in August 2021. At the time this analysis was conducted, data were only available through 2020.

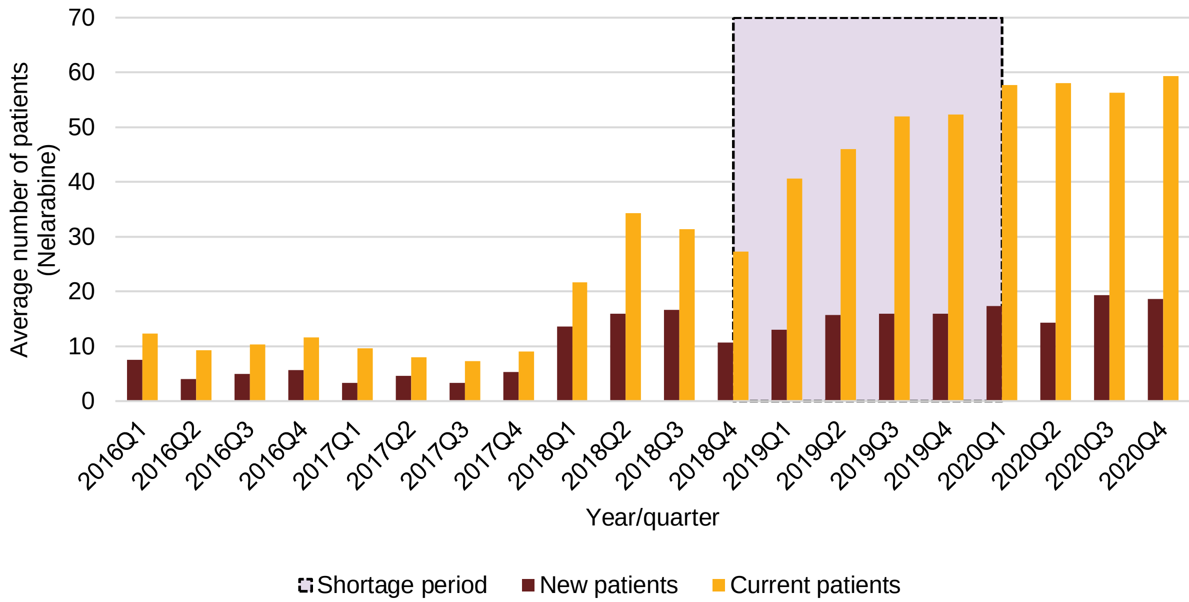
Appendix Exhibit 6: Number of New, and Current Users for Asparaginase (J9020)



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.

Note: Shortage period for asparaginase started in October 2016; shortage ended in August 2021. At the time this analysis was conducted, data for asparaginase (J9020) were only available through the third quarter of 2019.

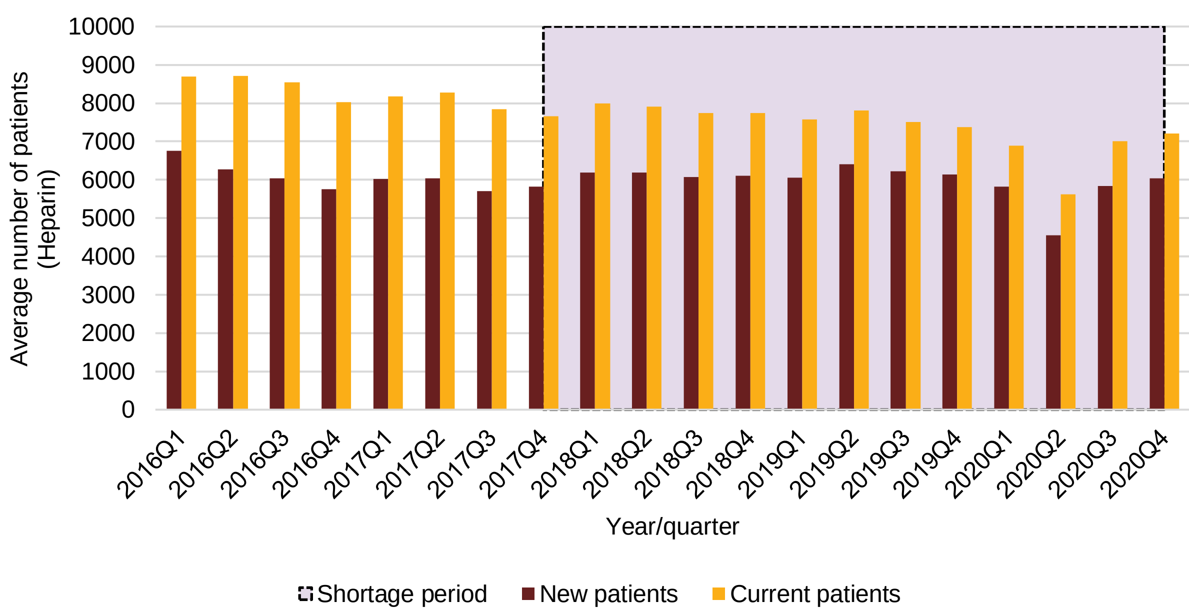
Appendix Exhibit 7: Number of New, and Current Users for Nelarabine



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.

Note: Shortage period for nelarabine was from October 2018 to January 2020. At the time this analysis was conducted, data were only available through 2020.

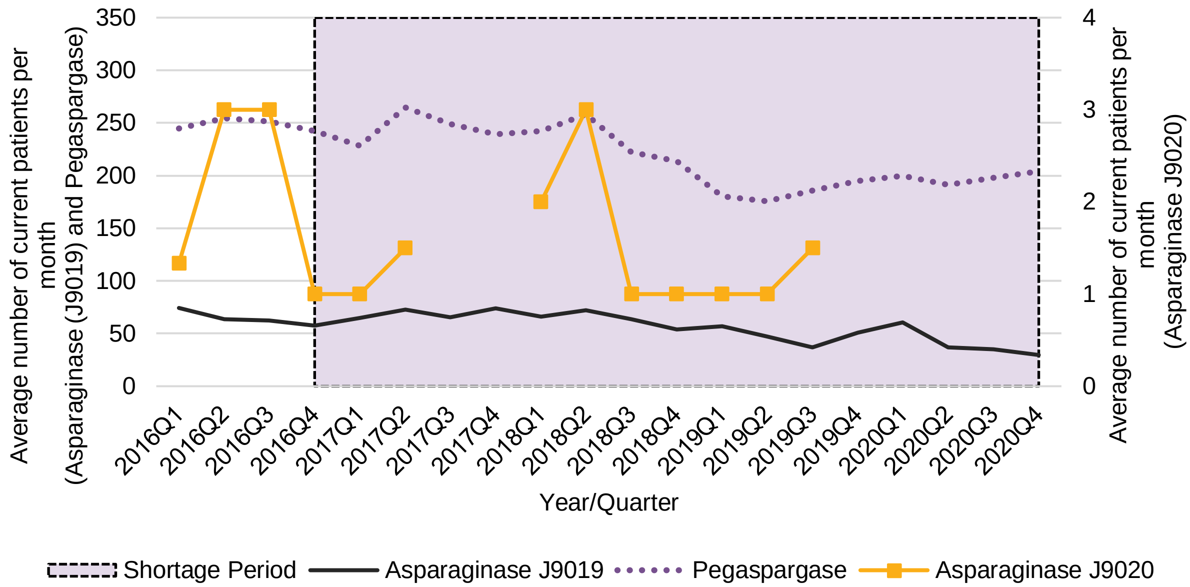
Appendix Exhibit 8: Number of New, and Current Users for Heparin



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.

Note: Shortage period for heparin started in November 2017; as of March 2024, this shortage was still ongoing. At the time this analysis was conducted, data were only available through 2020.

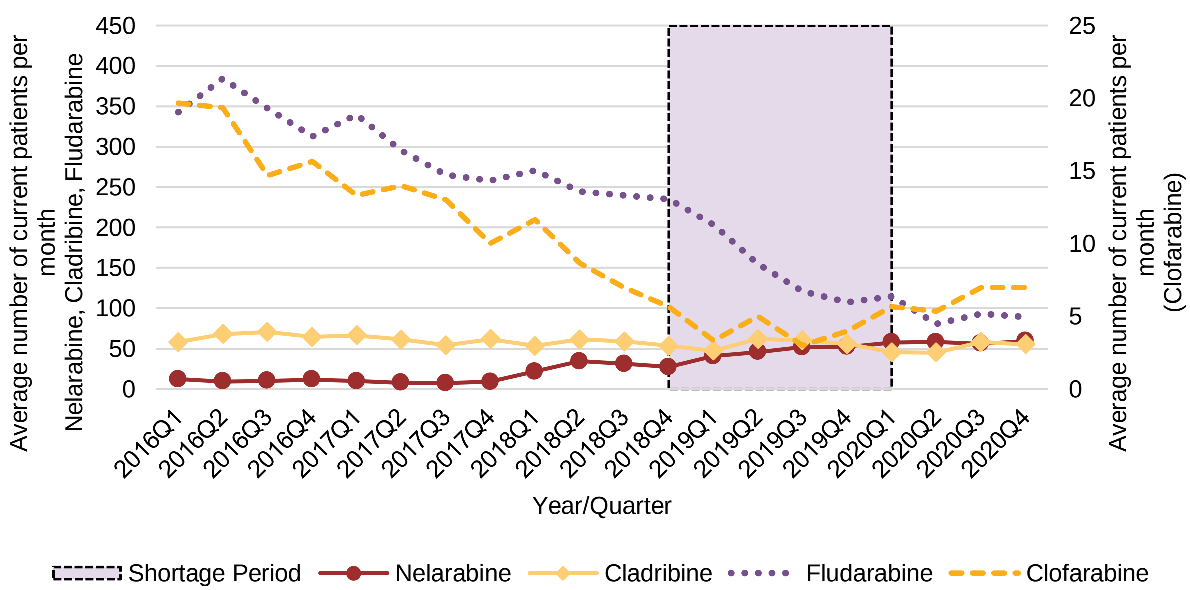
Appendix Exhibit 9: Number of Patients Using Asparaginase (J9019 & J9020) and its substitute



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.

Note: Shortage period for asparaginase started in October 2016; shortage ended in August 2021. At the time this analysis was conducted, data were only available through 2020, except for asparaginase (J9020) for which data were available through the third quarter of 2019.

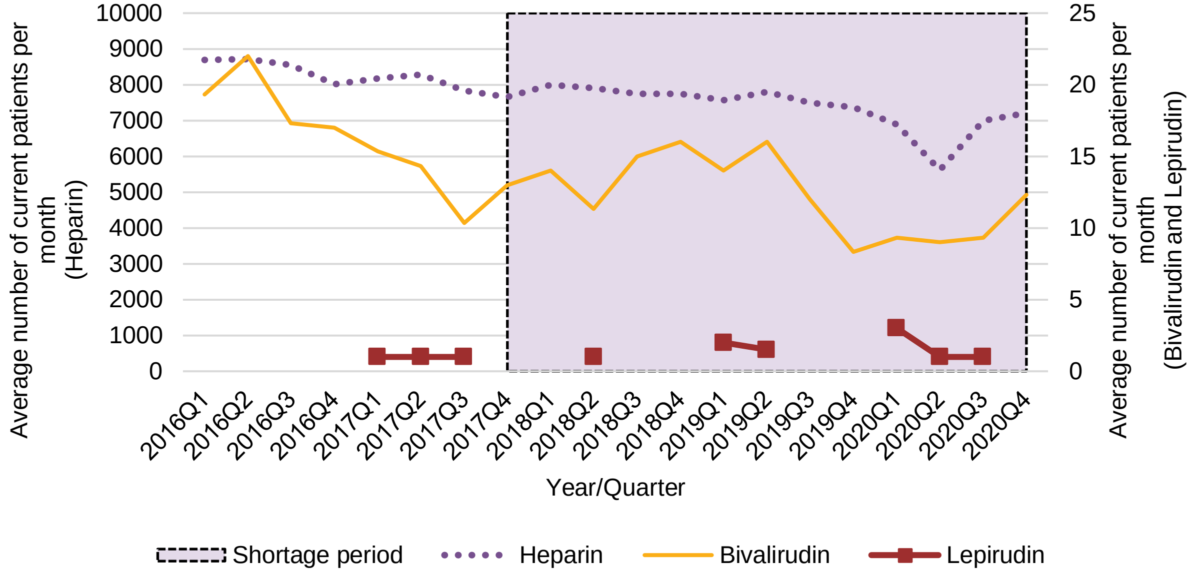
Appendix Exhibit 10: Number of Patients Using Nelarabine and its Substitutes



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.

Note: Shortage period for nelarabine was from October 2018 to January 2020. At the time this analysis was conducted, data were only available through 2020.

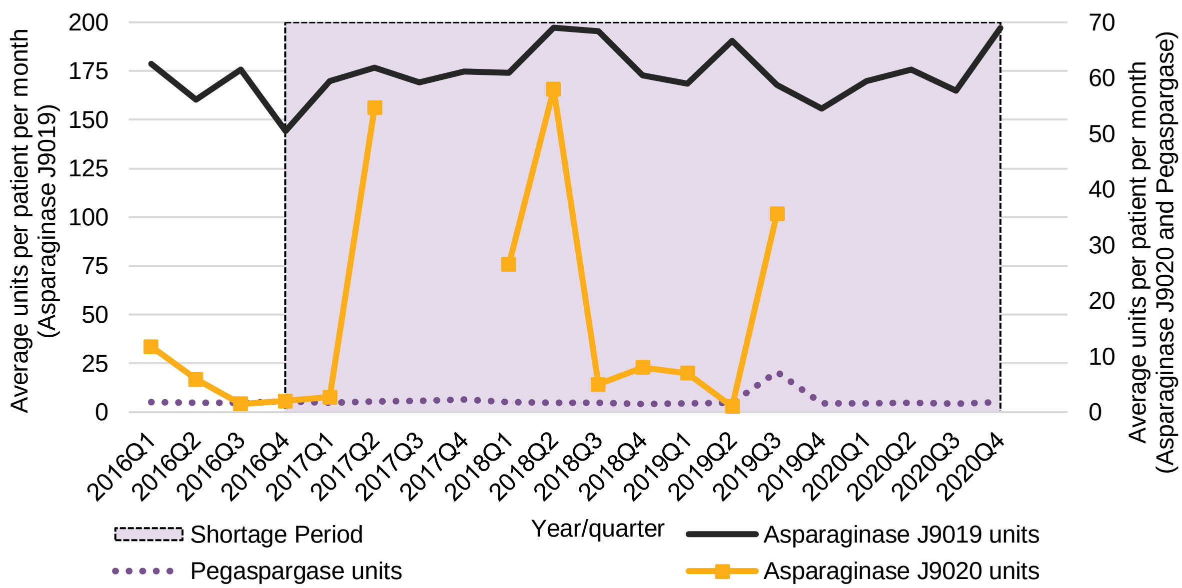
Appendix Exhibit 11: Number of Patients Using Heparin and its Substitutes



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.

Note: Shortage period for heparin started in November 2017; as of March 2024, this shortage was still ongoing. At the time this analysis was conducted, data were only available through 2020.

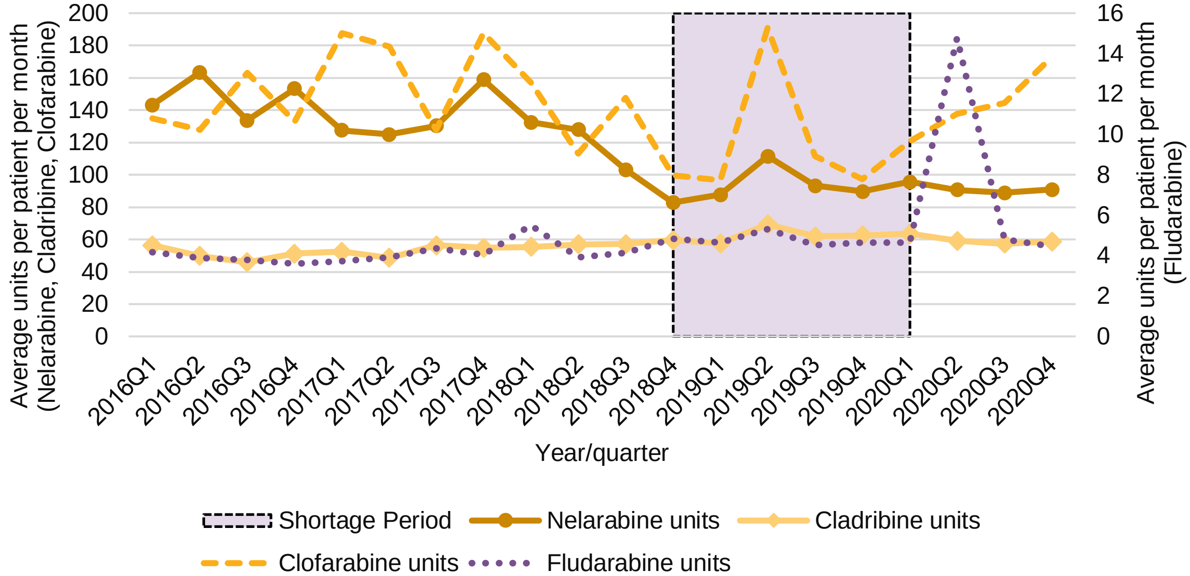
Appendix Exhibit 12: Service Units for Asparaginase (J9019) and Asparaginase (J9020) and their Substitute



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.

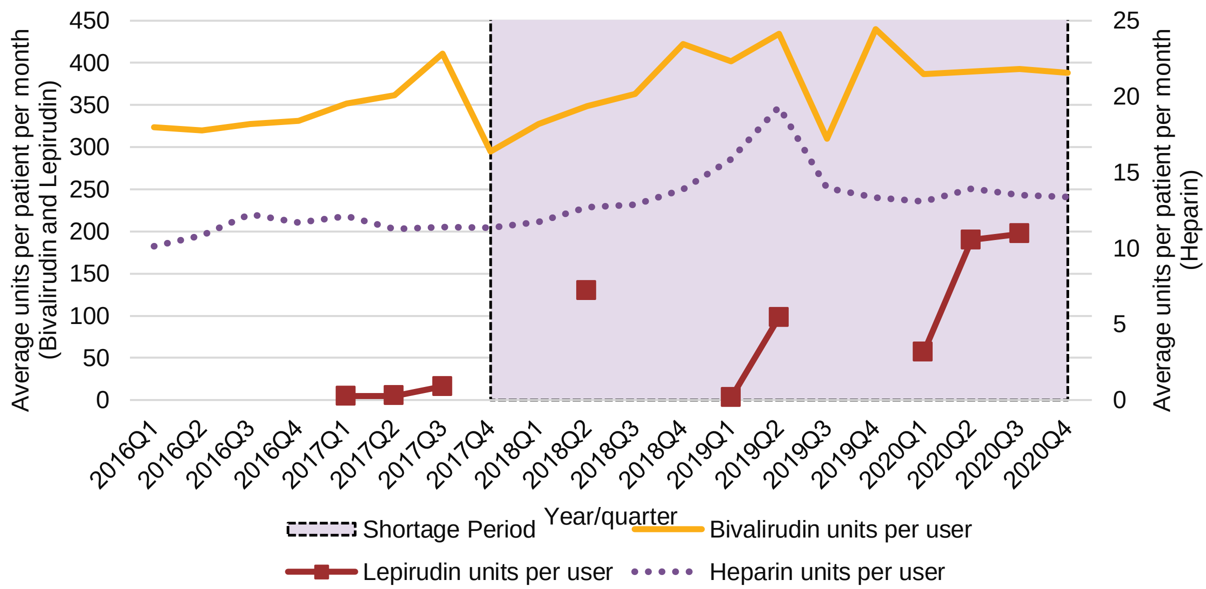
Note: Shortage period for asparaginase started in October 2016; shortage ended in August 2021. At the time this analysis was conducted, data were only available through 2020, except for asparaginase (J9020) for which data were available through the third quarter of 2019.

Appendix Exhibit 13: Service Units for Nelarabine and its Substitutes



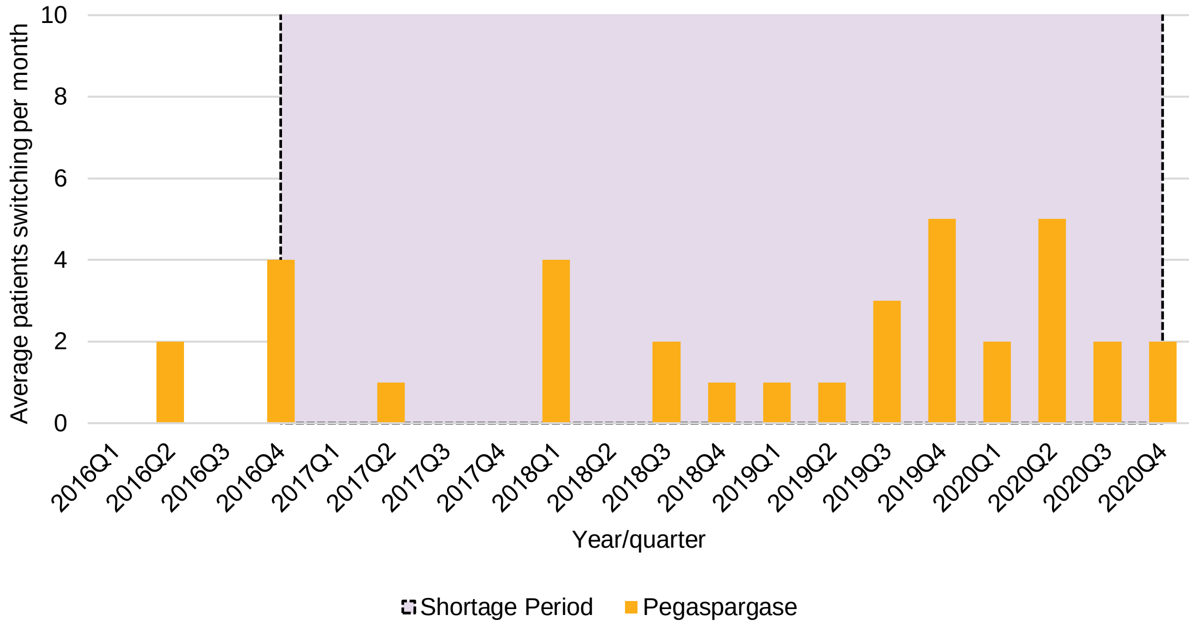
Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Note: Shortage period for nelarabine was from October 2018 to January 2020. At the time this analysis was conducted, data were only available through 2020.

Appendix Exhibit 14: Service Units for Heparin and its Substitutes



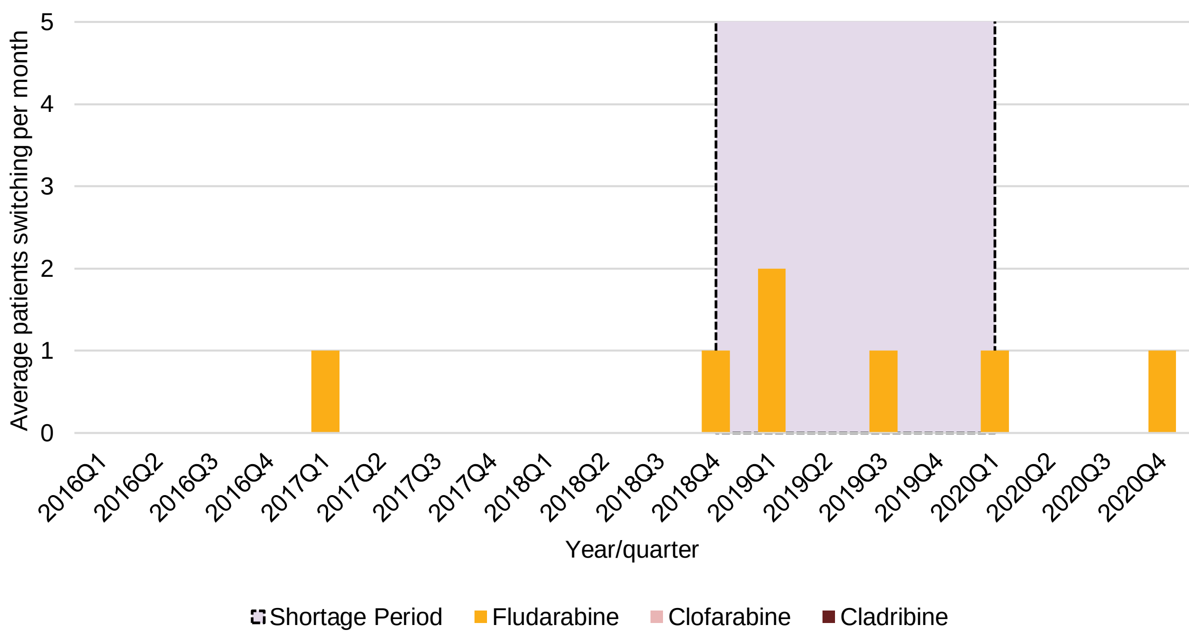
Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Note: Shortage period for heparin started in November 2017; as of April 2024this shortage was still ongoing. At the time this analysis was conducted, data were only available through 2020.

Appendix Exhibit 15: Asparaginase Patients that Switched to its Substitute (Pegaspargase)



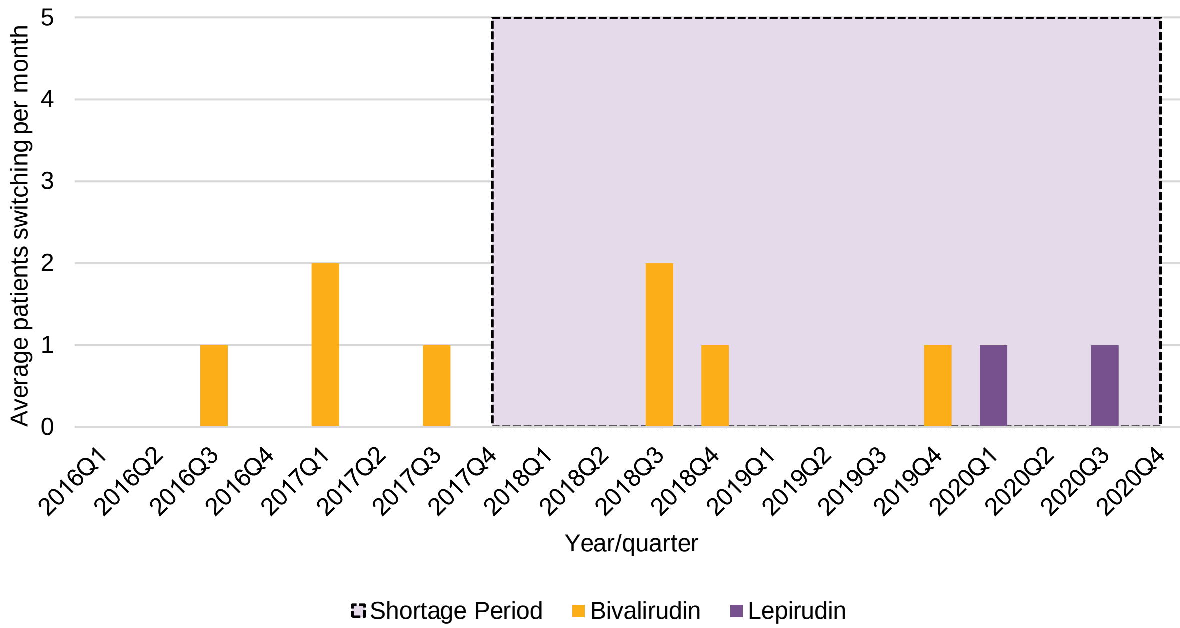
Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Note: Shortage period for asparaginase started in October 2016; shortage ended in August 2021. At the time this analysis was conducted, data were only available through 2020.

Appendix Exhibit 16: Nelarabine Patients that Switched to its Substitutes (fludarabine, clofarabine, or cladribine)



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.
Note: Shortage period for nelarabine was from October 2018 to January 2020. At the time this analysis was conducted, data were only available through 2020.

Appendix Exhibit 17: Heparin Patients that Switched to its Substitutes (bivalirudin and lepirudin)



Source: Authors' analysis of 2016 – 2020 IQVIA Dx data. Drug shortages are identified using the FDA Drug Shortages Database downloaded March 2020.

Note: Shortage period for heparin started in November 2017; as of April 2024, this shortage was still ongoing. At the time this analysis was conducted, data were only available through 2020.