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About the cover:
A review of literature sheds new light on the consistent cost savings associated with home and outpatient infusion therapy when compared to the inpatient site of care for a range of infused drugs.

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From the Editor

Documenting the Cost Savings Associated With Outpatient Infusion Therapy

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Editor-in-Chief, *Infusion Journal*

Understanding financial decisions for choosing the site of care for infusion therapy can leave patients and providers feeling like they are given limited options. Determining the proper site of care for infusion medication administration is a growing challenge with complex reimbursement decisions. Reimbursement for the same medication could be higher, lower, or not reimbursed due to where it was administered.[1] Too often, insurance benefit design and the patient's potential financial responsibility weigh heavily in the decision-making process.

When receiving a referral, home infusion providers are trained to assess the patient and treatment plan. The pharmacy and nursing team can evaluate the site of care based on clinical information and financial outcomes as part of coordinating care with the patient's insurance. Based on payor restrictions and patient characteristics, one of these locations may be a better option, either financially or clinically.

The care coordination model in home infusion has been effective in providing explanations of financial responsibilities to patients and keeping patients involved in their site of care decisions. NHIF collected patient satisfaction survey data and established home infusion industry benchmarks for satisfaction. For the question, "I understood the explanation of my financial responsibilities for home infusion therapy," the 2022 benchmark was 89.85% of patients who responded "yes" to understanding their financial responsibility for their home infusion therapy.[2,3]

As part of ongoing care coordination, the patient's eligibility is verified, and the treatment plan is updated. Data collected on the status of patients discharged from home infusion services reported higher rates of the reasons "change in eligibility" and "change infusion provider" in patients who were discharged for therapy types that included specialty drugs.[4,5] The increasing number of specialty medication approvals coupled with the high cost of these medications has become a target for reducing health care costs through site of care optimization.

Site of care costs will influence financial decisions. The article in this issue of *Infusion Journal* by Danell Haines, titled, Cost Savings: Home Versus Inpatient Infusion Therapy, A Review of the Literature, evaluated the current evidence available for cost comparison of infusion medications administered in the hospital setting compared to the home or alternate site. The literature review was specific to data collected in the United States since it would not be a balanced comparison to analyze U.S. health care cost results against other countries due to significant differences in the health care systems. The author's conclusions

found consistent cost savings associated with home and outpatient infusion therapy compared to the inpatient SOC for a range of infused drugs.

The author performed an extensive search with open search dates. From 1988 to 2023, only 6 articles met the inclusion criteria for the literature review. Four of the 6 compared outpatient anti-infective therapy (OPAT) to inpatient or hospital-based care. The author provided a count of excluded articles from outside the U.S., and it is worth noting that the amount of research available from single payor systems was more widely published.

While Haines' findings do not come as a surprise for home and alternate site infusion professionals, there is an obvious need for research in reimbursement and cost analyses of health care by site of care.

Promoting evidence-based research is at the heart of our mission, and *Infusion Journal* is interested in publishing cost-related research in home infusion. As the pipeline of specialty infusion medications grows, it represents an area for large savings and an opportunity for site of care research. *Infusion Journal* maintains a list of suggestions for research in relevant areas of interest in home infusion.[6]

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Cost Savings: Home Versus Inpatient Infusion Therapy, A Review of the Literature

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ABSTRACT

Introduction

Home infusion is a site of care (SOC) option for patients requiring intravenous (IV) or subcutaneous (SC) medications for treatment of acute and chronic medical conditions. Patients and payors have become aware of the sizeable cost savings associated with home infusion compared to other SOCs. There is a need to understand the amount of savings associated with home infusion compared to other SOCs such as the hospital. The literature review objective is to provide a critical evaluation of the current evidence of the cost savings associated with home and outpatient infusion therapy when compared to inpatient therapy.

Methods

The literature search was conducted between July 1, 2023, and August 2, 2023, and focused on terms related to home infusion, home-based, homecare, outpatient, or infusion followed by cost, cost comparison, cost savings, or SOC optimization. PubMed through the National Library of Medicine was searched. After reviewing the articles, it was determined that it is not feasible to compare U.S. health care cost results to other countries due to significant differences in health care systems, financial resources, and co-payment systems, thus studies conducted outside of the U.S. were excluded.

Results

Six articles met the review inclusion criteria. The first article was a cost analysis of a home infusion antibiotic program and showed that the savings per home infusion patient was $40,460 when compared to inpatient costs. Another article investigated the cost of home and inpatient antibiotic infusion and determined that the cost per day for home infusion was $122 while the cost for inpatient was $798. The third article calculated the cost difference of home infusion enzyme replacement with inpatient therapy and concluded a significant difference ($p \leq .0001$) existed between the SOC costs. One study focused on developing a cost model using patient care information that included Medicare data. The model showed a cumulative 5-year savings of over $3 billion in 2023 health care dollars. The last article compared the home and inpatient infusion cost of inotropic therapy for patients awaiting heart transplant and concluded that the home infusion savings was $71,300 to $120,500 per patient.

Discussion

The reviewed studies demonstrate significant cost savings when the home is the SOC for infusion therapy, especially for IV antimicrobial treatment. This is significant as IV antibiotic therapies comprise nearly half of all treatments done at home today. One study provides evidence for savings associated with enzyme replacement; a therapy analogous to the growing number of specialty biologics being used today to manage chronic diseases. Despite evidence of cost savings, Medicare has not developed a home infusion benefit comparable to what is available in the private sector.

Conclusions

The literature review provides evidence of consistent cost savings associated with home and outpatient infusion therapy compared to the inpatient SOC for a range of infused drugs. The study with the most rigorous methodology involved a model that showed a 5-year Medicare savings of $3 billion in today's dollars with the implementation of a home infusion antibiotic therapy Medicare benefit.

Keywords: Home Infusion, Site of Care, Cost, Medicare, Homecare

Introduction

Home infusion is a site of care (SOC) option for patients requiring intravenous (IV) or subcutaneous (SC) medications for treatment of acute and chronic medical conditions, ranging from bacterial infections to heart failure, nutrition support, cancer, and autoimmune diseases. Home infusion is well established, having been in place for more than 4 decades spurred primarily by commercial insurance plans that capitalize on the cost savings of administering IV and SC infused treatments at home rather than in facility-based settings. The increased number of infused therapies, improved access devices, patient preference for home-based care, coupled with a well-established commercial reimbursement pathway has prompted consistent growth of home infusion within the context of the health care market. In 2010, the National Home Infusion Association (NHIA) reported that infusion providers served 829,000 unique patients, whereas in 2019, this number grew to more than 3.2 million, representing a growth of 310%.[1]

The popularity of home infusion is due to many factors. It includes the growing confidence that physicians have in the home infusion process, comparable clinical outcomes, and improved quality of life reported in the literature.[2] Additionally, patients and payors have become aware of the sizeable cost savings associated with home infusion when compared to other SOCs. This concept is often referred to as a SOC optimization strategy. With costs related to a growing class of infused specialty drugs continuing to increase, there is a need to understand the savings associated with home infusion compared to other SOCs, such as the hospital where these drugs and biologics tend to be infused. In addition to research studies, many companies have published reports demonstrating cost-savings and improved outcomes associated with SOC optimization programs. For example, United Health Care and Cigna have touted the savings achieved through SOC programs. Medicare aims to divert some therapies to the home by designating drugs as "usually self-administered".[3,4] To meet this need, this review summarizes the research on the cost savings associated with home and outpatient infusion when compared to the inpatient SOC.

The last known review of the literature on the inpatient-outpatient infusion cost comparison was reported in 2017, conducted in Brazil, and focused only on anti-infective therapy.[5] In the U.S., the same type of review was reported in 1989, and concluded that all studies in the review showed cost savings in the outpatient SOC.[6] There is a plethora of reported research in other countries on the cost differences of outpatient and inpatient infusion, with the home and outpatient SOC showing significant savings.[7-11]

The objective of this literature review is to provide critical evaluation of the current evidence of the cost savings associated with home and outpatient infusion therapy when compared to inpatient therapy. SOC optimization applied to home infusion involves patients moving away from high-cost health facilities, such as hospitals, to lower-cost settings, such as home infusion. As stated by Tsai and Doherty, "Effectively, the success of population health management has hinged on SOC optimization in an effort to provide the highest quality care at the lowest cost SOC."[12] This review will evaluate published studies that examine whether home infusion as a SOC optimization strategy is associated with cost savings in the U.S., and whether implementing such a benefit for Medicare would be likely to generate cost savings for the government.

Methods

The literature search was conducted between July 1, 2023, and August 2, 2023, and focused on terms related to home infusion, home-based, homecare, outpatient, or infusion followed by cost, cost comparison, cost savings, or SOC optimization. PubMed through the National Library of Medicine was searched. This search engine comprises more than 35 million citations for biomedical literature from MEDLINE, life science journals, and online books. This search produced 18 journal articles of which 14 included cost data from studies conducted outside of the U.S. After reviewing the articles, it was determined that it is not feasible to compare U.S. health care cost results to other countries due to significant differences in health care systems, financial resources, and co-payment systems, thus studies conducted outside of the U.S. became an exclusion criterion. The number of journal articles meeting the inclusion criteria was reduced to 4, thus reference lists from the original 18 articles were reviewed to determine if other U.S. home infusion cost comparison studies existed. Two additional reported studies were located and considered appropriate for the review.

TABLE 1 | Literature on Home/Outpatient and Inpatient Infusion Cost Comparison

First Author	Year	Therapy & Study Type	Site Comparison	Results
Chamberlain TM[13]	1988	Anti-infective retrospective chart and billing review	Inpatient vs home infusion	Home infusion mean total cost savings per patient = $40,460
Dalovisio JR[14]	2000	Anti-infective retrospective chart review of home infusion pts vs theoretical cost of inpatient	Inpatient vs home infusion	Home infusion mean cost per day = $122 Inpatient mean cost per day = $798
Stewart A[15]	2017	Enzyme replacement retrospective chart review	Inpatient vs home infusion	There was a significant difference ($p \leq .0001$) in cost between inpatient and home infusion. Home infusion mean cost per day = $225.10, hospital mean cost per day = $586.50.
Ruh CA[16]	2015	Anti-infective retrospective chart review	Inpatient vs rehab care vs home infusion	Mean total cost savings for home infusion patients was $81,559 when compared to inpatient cost.
Tice A[17]	1998	Anti-infective cost model to determine a Medicare 5-year cost savings if home infusion coverage was implemented		The model shows cumulative 5-year savings of nearly $1.5 billion.
Upadya S[19]	2004	Inotrope comparative cost study (patients awaiting transplantation)	Inpatient vs home infusion	Outpatient strategy saved a total of $71,300 to $120,500 per patient

Results

As shown in Table 1, 6 articles met the inclusion criteria for this review and differed in terms of methods used, types of costs, SOC, and patient populations of interest. Most of the articles use the term "outpatient" which is a broad term that includes SOCs that do not require a hospital admission while inpatient includes a hospital admission. The articles are discussed in the order presented in Table 1.

The first article is a cost analysis of a home infusion anti-infective program for patients with osteomyelitis and was conducted by Chamberlain, et al. using patients' billing records and charts. The cost savings per home infusion patient was $40,460 when compared to inpatient costs.[13] Dalovisio, et al., also investigated the cost of home and inpatient anti-infective infusion.[14] A retrospective chart review compared home infusion cost to an inpatient theoretical cost. The aim of the study was to show the financial impact of a home infusion anti-infective program on a Medicare managed care program. It was determined that the cost per day for home infusion was $122 while the cost for inpatient was $798. The total cost of the 66 courses of anti-infective therapy, encompassing 1,542 patient days was $188,663. The estimated savings ranged from $646,000 to $871,000 when the home was the SOC.

Stewart et al. investigated the cost difference of home infusion enzyme replacement with inpatient therapy and concluded that there was a significant difference ($p \leq .0001$) between the home and inpatient cost.[15] Home infusion and inpatient mean cost per day were $225.10 and $586.50, respectively. Another antibiotic pharmacoeconomic analysis was conducted by Ruh, et al. using billing records.[16] The study concluded that home infusion is an efficient and cost-effective method of treating patients who require long-term antimicrobial therapy. Furthermore, it was reported that the mean total cost savings for each home infusion patient was $81,559 when compared to inpatient cost.

Tice, et al. aimed to develop a cost model using patient care information that included Medicare data, to determine the 5-year savings associated with a home infusion antibiotic therapy Medicare benefit.[17] The investigators were meticulous in their study design and approach. They determined that the

model shows a cumulative 5-year savings of nearly $1.5 billion, which in 2023's health care dollars would equate to more than double the amount and be over $3 billion.[18] Finally, Upadya, et al. compared the home and inpatient infusion cost of inotropic infusion therapy for patients waiting for cardiac transplantation and concluded that home infusion realized an average savings of $71,300 to $120,500 per patient compared to inpatient infusion therapy.[19]

Study Limitations

The article with the most robust methodology and analytical precision was conducted by Tice, et al. and involved a model that showed a 5-year Medicare savings of $3 billion in today's dollars with the implementation of a home infusion antibiotic therapy Medicare benefit. Although the other studies demonstrate cost savings when the home is the SOC for infusion therapy, the ability to extrapolate the savings to the wide range of therapies provided today is compromised by mediocre research methodological quality. Additional economic assessments of the cost of infusion therapy are needed using more rigorous methodologies that include a broad range of perspectives to identify the real magnitude of the economic savings when the home is the SOC instead of the hospital, particularly for modern treatments that involve specialty drugs. Even so, all reviewed studies showed considerable cost savings when the home is the SOC.

Discussion

The objective of this literature review was to provide critical evaluation of the current evidence of the cost savings associated with home and outpatient infusion therapy compared to inpatient therapy. The reviewed studies, although limited, demonstrate significant cost savings when the home is the SOC for infusion therapy, especially for IV anti-infective treatment. This is significant as IV anti-infective therapies comprise nearly half of all treatments done at home today.[1] The study by Stewart, et al. provides evidence for savings associated with enzyme replacement, a therapy analogous to the growing number of specialty biologics being used today to manage chronic diseases.[15] Numerous studies have examined the clinical benefits of home infusion as a driver for increased utilization, however few have analyzed the cost savings associated with shifting care to the home.

Over the past decade, the growth in home infusion has been impacted by commercial payors seeking to lower the overall costs associated with administering IV treatments. Broader provider experience and patient preferences for more convenient treatment options are also contributing factors. Despite evidence of cost savings and increased patient satisfaction, Medicare has not developed a home infusion benefit comparable to what is available in the U.S. private sector. In December 2016, the 21st Century Cures Act was enacted into law to establish a new Medicare home infusion benefit.[20] However, the Centers for Medicare and Medicaid Services (CMS) limited reimbursement to services "only on days when a nurse is present in the patient's home," which is typically once a week, leaving significant gaps in coverage for essential pharmacy-related professional services that take place remotely.[21] SOC choices for Medicare beneficiaries are generally limited to Part A and Part B facility-based settings. Patients who elect home infusion over other SOC settings (i.e., hospital, skilled facility, physician office, hospital outpatient department) must bear the financial burden of paying out of pocket for the costs of supplies and professional pharmacy services (IV drugs are often covered by Part D). This review suggests that Medicare could achieve as much as $3 billion in savings by providing more comprehensive access to home infusion.

Conclusions

The literature review provides evidence of consistent cost savings associated with home and outpatient infusion therapy when compared to the inpatient SOC for a range of infused drugs. The study with the most rigorous methodology was conducted by Tice, et al. and involved a model that showed a 5-year Medicare savings of over $3 billion in today's dollars with the implementation of a home infusion anti-infective therapy Medicare benefit.[17]

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Development of Productivity Standards for Ambulatory Infusion Suite Nurses Within a Multi-Entity Health System

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ABSTRACT

Introduction

A productivity metric that infusion sites measure to gauge operations is chair capacity, which is a direct reflection of physical chair utilization based on the inputs of total time patients occupy chairs and total time the chair is available (i.e., hours of operation multiplied by chair count). Although a convenient metric, it does not capture all relevant information, and there is a need to identify standard metrics that account for infusion nurse workload. Minimal literature currently exists that describes specific methods for obtaining more accurate clinician-focused capacity metrics that could better track productivity and staffing needs for successful operations. The purpose of this project is to identify metrics that will account for clinician-focused capacity and use them to create an operational tool that ambulatory infusion suites (AISs) can utilize to relay productivity and business standards.

Methods

Two time studies were conducted across 3 AIS locations within our organization: (1) an in-person time study of 7 nurses observing of all performed tasks (including both clinical and non-clinical care) over approximately 52 hours; and (2) an electronic time study looking at electronic health record (EHR) appointment reports (infusion therapy, appointment length, patient check-in time, and discharge time) over a 1-month period (n=407). Data from the 2 time studies were used to develop and validate metrics and metric parameters for an infusion nurse productivity scorecard.

Results

From the in-person time study, 50 distinct tasks were identified and grouped into categories (Operations, Direct Patient Care, Indirect Patient Care, Medications, Documentation, Communications, and Other). Assuming an 8.5-hour workday, nurses were estimated to spend similar amounts of time in Communications (76.5 min), Direct Patient Care (81.6 min), Documentation (86.7 min), and Indirect Patient Care (96.9 min). Amongst individual tasks, patient chart checks (40.8 min), and appointment scheduling (35.7 min) occupied the most time. Analysis of patient encounters from EHR informed proposals to shorten, extend, or make no changes to appointment lengths for different treatments. The productivity scorecard comprised specific tasks, allotted points, and goal number of points for nurses to achieve daily. Testing of the scorecard via retrospective grading on 5 full-day time studies determined 15 points' worth of tasks a day for a nurse to be considered "productive."

Implications/Conclusions

The time studies highlighted trends and potential areas of improvement in AIS nurse workflow, scheduling, and resource needs. The creation of the operational scorecard tool will allow AIS management to better evaluate productivity during business performance reviews. Adoption across all infusion centers within our organization would be ideal; however, it is unclear if operational differences at non-studied AIS locations may affect standards and should be tested prior to universal adoption. Additionally, this project specifically focused on infusion nurses, and further research is needed to identify similar items for other AIS personnel (e.g., pharmacists, medical assistants). Overall, capacity within AIS should be measured by both physical chair utilization and clinician-focused consideration. Development of a tool that accounts for personnel capacity will better inform operational limits and opportunities.

Keywords: ambulatory infusion suite, time study, nurse productivity

Introduction

Ambulatory infusion suites of the home infusion therapy provider, otherwise known as ambulatory infusion suites (AISs), have become emergent health care facilities. As alternative sites of care to hospital settings, AIS sites facilitate logistics for patients to receive clinical care from infusion personnel—often infusion nurses and pharmacists—pursuant to physician orders for administration of infusion or specialty drugs.[1] Since the 1980s, the home infusion and alternate site infusion industry has seen tremendous growth. In 2019, home infusion and alternate site providers cared for more than 3.2 million patients in the United States, which represented a three-fold increase since 2008.[2] The safety, effectiveness, and cost savings associated with these alternative sites make them highly attractive options for patients with both acute and chronic conditions that cannot be effectively treated with oral medications alone.

With more patients choosing to receive care in AIS sites, these sites strive to provide services to as many patients as possible. To meet this goal, it is beneficial for AIS sites to capture metrics to trend patient volume, which can in turn help gauge the productivity of AIS site operations. Metrics can also potentially inform business decisions to expand AIS site capacity, such as whether to add more infusion chairs or even clinical resources. In addition, these metrics can be used as a surrogate for AIS site management to track the productivity of infusion personnel and monitor staffing needs.

The most common metric used to measure productivity of AIS sites is chair capacity. Chair capacity is a direct reflection of physical infusion chair utilization. It is based on 2 inputs: the total time patients occupy infusion chairs and the total time the chairs are available. Calculating the total available infusion chair time can be found by multiplying the AIS site's hours of operation by the total chair count (Figure 1).[3] For example, an AIS site that is open from 9:00 AM to 5:00 PM and has 10 infusion chairs would have a total of 80 available chair hours per day. If 9 patients showed up 1 day, and each needed a 6-hour infusion (e.g., starting from taking premedications 30 minutes prior to starting infusion, running the infusion, and staying for an additional 30 minutes for observation), the total amount of patient-occupied chair time would be 54 hours that day. Utilizing the calculation in Figure 1, 54 hours of the possible 80 would be utilized and the day's chair capacity would be 67.5%.

FIGURE 1 | Formulas for Calculating Chair Capacity

$$\text{Chair Capacity} = \frac{\text{Total Hours of Patients in Chairs}}{\text{Total Available Chair Hours}}$$

Total Available Chair Hours = Hours of Operation x Total Chair Count

The simplicity of the theory behind chair capacity makes it an easy-to-use and easy-to-understand metric to show productivity. The total available chair-hours represent the theoretical maximum number of hours of infusions that the site can provide; if the site wished to offer more hours, it must increase the number of hours of its operations, add additional infusion chairs, or both. The optimal chair capacity that AIS sites strive to reach is as close to 100% as possible, to allow AIS sites to maximize the number of patients seen while minimizing vacancies between infusion appointments. However, it is generally not realistic to schedule patients such that when 1 patient arrives for an infusion, the person who had been occupying that specific chair will have just completed their appointment. According to the 2019 Infusion Center Volumes, Staffing, and Operations Survey, the median daily scheduled chair utilization rate was 80%, and the median actual chair utilization rate was 70%.[4]

It is worth noting the drawbacks of chair capacity, even as it is the mainstay of AIS productivity measurement. First, chair capacity does not necessarily consider variability in the day. A full schedule may change because of appointment rescheduling, canceling, patient no-shows, or walk-ins. These changes may happen at any time and cannot easily be predicted. Although chair capacity would increase or decrease accordingly, it would not be able to provide an explanation on why the percentage was higher or lower than expected. Second, the sole number that chair occupancy presents can be misleading. The amount of time that a patient is sitting in an infusion chair may not necessarily equate to the amount of quality care they are receiving. Results of the 2014 National Hospital Oncology Benchmark for Infusion found that infusion chairs are utilized for active treatment only 18% of the total chair time available.[5] Third, while it may seem that patients sit idly in infusion chairs for more than 80% of their time, it should be mentioned that infusion personnel, such as infusion nurses, are completing a multitude of tasks in the background. For example, infusion nurses are involved in communications, education, medication administration, and documentation, and they are often rapidly shifting between tasks or multitasking.[6] Chair capacity gives no indication of this behind-the-scenes work. Thus, it is important to comprehend what is happening beyond the physical infusion chair.

We argue that chair capacity's ability to provide deeper insight into AIS operations and productivity is limited. We propose the need to pivot away from chair capacity to a different kind of metric, which we call "clinician-focused capacity." There is a need for metrics that can measure productivity not only more comprehensively, but also with an actionable level of detail. Instead of focusing on physical chair utilization, the focus should be on the infusion personnel who are orchestrating patient care and treatment. We believe that clinician-focused capacity, which would measure productivity based on the tasks that infusion personnel spend their time on each day, would better inform AIS management on productivity. Clinician-focused capacity would paint a bigger picture of daily operations, as well as provide information to analyze where improvements in AIS site workflow can be made.

Unfortunately, minimal literature describes specific methods on how to collect data to measure productivity of infusion staff, not to mention standard metrics related to clinician-focused capacity. Some literature exists on the optimization of patient flow in infusion centers—specifically oncology infusion centers.[7,8] However, there is minimal published literature that focuses on the workflow of infusion personnel. Additionally, there is little to no published literature on the study of workflow in non-oncology infusion suites.

Because of this lack of available information, we decided to develop a study to build out the concept of clinician-focused capacity. The intent of this project was to first identify a standardized set of tasks that can account for clinician-focused capacity, and in turn create an operational tool that AIS sites can use to inform productivity and business standards. Our goal was to provide a framework for AIS sites to use and begin incorporating clinician-focused capacity into their productivity metrics.

We note that this study specifically focused on developing clinician-focused capacity metrics with respect to infusion nurses. However, this study can be expanded to study other infusion personnel (e.g., pharmacists, pharmacy technicians, medical assistants) in the future.

Methods

To meet our objective to develop clinician-focused capacity metrics focused on infusion nurses, we performed 2 sets of time utilization studies. Time utilization studies (also known as time-and-motion studies; herein referred to as "time studies") are commonly performed in health care settings to attain detailed observations of workers to determine the time required to accomplish specific tasks. These observations are ultimately used to assess and optimize quality, efficiency, and costs in health care delivery.[9]

To assess infusion nurse workflow at the AIS sites at Johns Hopkins Home Care Group (herein referred to as "our organization"), we performed time studies at our 3 non-oncology, non-gastrointestinal AIS sites. Our rationale for starting with these 3 sites was because they were operated solely by infusion nurses; these sites would be the simplest to observe before expanding our studies to other infusion sites with other infusion personnel.

In-Person Time Study

An in-person time study was performed on the full-time infusion nurses that staffed across our 3 selected non-hospital AIS sites. Before conducting the time studies, informal observing was first completed to identify distinct tasks that infusion nurses performed over the course of the day, including tasks related to clinical care and non-clinical care. All tasks were then compiled and standardized into a single list. This list was referenced during the formal observation (e.g., time study), so documentation of infusion nurse actions would be consistent across all formal observations.

An Excel spreadsheet was developed to record the specific task performed by the observed infusion nurse, as well as automatically capture the date and time (formatted as MM/DD/YY HH:MM:SS using an Excel macro) when the action started and when it ended. This information was used to calculate the duration of time spent on each task performed. The lead author conducted time studies on all the full-time infusion nurses. The data were then aggregated to calculate the total amount of time spent on each distinct task across the entire observation period. The information was then scaled to extrapolate how much time it would be expected to spend on each task in 1 business day (e.g., 8.5 hours).

Electronic Time Study

An electronic time study was performed to measure the duration of time of historical infusion appointments. The same 3 AIS sites that were studied as part of the in-person time study were also selected for the

electronic time study. Reports of completed patient appointments over the course of 1 month (May 2022) at the 3 sites were generated from our electronic health record (EHR) system provider (Epic). The following information was extracted from the reports: type of infusion therapy, duration of scheduled appointment length, patient check-in time, and patient discharge time. The latter 2 parameters were used to calculate the actual duration of appointment length for comparison against the originally scheduled length. This information was used to determine the optimal length of appointments for different infusion therapies.

TABLE 1 | Ambulatory Infusion Nurse Tasks and Time Spent on Tasks

Task	Total Time Observed (H:MM:SS) (%)	Extrapolation to 8.5-Hour Day (minutes)
Communications	**7:40:27 (14.8)**	**71.4**
Answer phone call	0:44:44 (1.4)	5.1
Check email	1:17:36 (2.5)	10.2
Talk with another nurse	2:25:30 (4.7)	25.5
Talk with another team member	1:50:49 (3.6)	20.4
Talk with doctor	0:25:27 (0.8)	5.1
Talk with pharmacy	0:10:51 (0.3)	0.0
Talk with supervisor	0:45:30 (1.5)	5.1
Direct Patient Care	**8:22:22 (16.2)**	**81.6**
Check in on patient	1:41:30 (3.3)	15.3
Conduct pre-infusion assessments	0:52:34 (1.7)	10.2
De-access IV	0:34:33 (1.1)	5.1
Draw labs	0:27:33 (0.9)	5.1
Insert IV or access port	2:26:50 (4.7)	25.5
Patient medication reaction	0:00:00 (0.0)	0.0
Patient observation/ monitoring	0:45:49 (1.5)	5.1
Patient teaching/ education/AVS	0:00:00 (0.0)	0.0
Take vitals	1:33:33 (3.0)	15.3
Documentation	**8:48:23 (17.0)**	**86.7**
Complete labs paperwork	0:36:39 (1.2)	5.1
Document ADR	0:00:00 (0.0)	0.0
Document IV assessment	0:59:12 (1.9)	10.2
Document pre-infusion assessment	0:43:55 (1.4)	5.1
Document vitals	1:55:05 (3.7)	20.4
Fill out patient wrap-up	0:20:34 (0.7)	5.1
Update MAR	1:37:27 (3.1)	15.3
Update REMS program	0:06:55 (0.2)	0.0
Write patient note	2:28:36 (4.8)	25.5

Task	Total Time Observed (H:MM:SS) (%)	Extrapolation to 8.5-Hour Day (minutes)
Indirect Patient Care	**9:33:06 (18.4)**	**91.8**
Call patient	0:46:06 (1.5)	5.1
Patient troubleshooting	0:53:30 (1.7)	5.1
Release orders	0:16:57 (0.5)	5.1
Review patient chart	4:01:28 (7.8)	40.8
Scheduling	3:35:05 (6.9)	35.7
Medications	**5:27:16 (10.5)**	**56.1**
Administer hydration	0:17:12 (0.6)	5.1
Administer infusion	1:16:06 (2.4)	10.2
Administer injection	0:02:55 (0.1)	0.0
Administer pre-medications	0:25:36 (0.8)	5.1
Prepare hydration	0:24:09 (0.8)	5.1
Prepare infusion	2:30:00 (4.8)	25.5
Prepare injection	0:00:49 (0.0)	0.0
Prepare pre-medications	0:30:29 (1.0)	5.1
Operations	**8:30:18 (16.6)**	**76.5**
Clean patient area	1:44:37 (3.4)	15.3
Closing	0:32:41 (1.1)	5.1
Drop off tubes at laboratory	0:21:25 (0.7)	5.1
Opening	2:11:22 (4.2)	20.4
Order supplies	0:11:15 (0.4)	0.0
Organize medications/ supplies delivery	1:27:44 (2.8)	15.3
Patient admission	1:13:46 (2.4)	10.2
Restock supplies	0:47:28 (1.6)	5.1
Other	**03:24:48 (6.6)**	**30.6**
Attend meeting	0:13:06 (0.4)	0.0
Take break	1:32:54 (3.0)	15.3
Take lunch	0:52:37 (1.7)	10.2
Use bathroom	0:46:11 (1.5)	5.1

Abbreviations: ADR = adverse drug reaction; AVS = after visit summary; IV = intravenous; MAR = medication administration record; REMS = Risk Evaluation and Mitigation Strategy.

Development of Infusion Nurse Productivity Scorecard

Results from both the in-person and electronic time studies, as well as input contributed by infusion nurse staff, were used to develop an infusion nurse productivity scorecard.

Results

Identification of Distinct Infusion Nurse Tasks

From the informal observation, a total of 50 distinct tasks performed by infusion nurses were identified (Table 1). For the formal observation (i.e., the in-person time study), a total of 7 full-time infusion nurses were observed across 3 AIS sites. The total observation period was approximately 52 hours (51 hours, 46 minutes, and 40 seconds). The amount of time that infusion nurses were observed performing each of the 50 tasks is detailed in Table 1. Additionally, Table 1 displays the amount of time expected to be spent on each task during a single workday (e.g., 8.5 hours), which was calculated in proportion to the total observation time. Amongst the list of 50 tasks, patient chart checks and appointment scheduling occupied the most time (40.8 min and 35.7 min, respectively, in an 8.5-hour workday).

For ease of analysis, the 50 tasks were grouped into larger categories: Operations, Direct Patient Care, Indirect Patient Care, Medications, Documentation, Communications, and Other. A breakdown of how much time nurses were observed to spend on each category is provided in Figure 2. Assuming an 8.5-hour workday, nurses were estimated to spend roughly similar amounts of time in Communications (76.5 min), Direct Patient Care (81.6 min), Documentation (86.7 min), and Indirect Patient Care (96.9 min).

Optimization of Patient Appointment Lengths

A total of 407 patient appointments across 34 types of infusion or injectable therapies, offered at the 3 AIS sites, were analyzed (Table 2). Upon comparison of the scheduled appointment length to the actual appointment length (e.g., time from patient check-in to patient discharge), it was noted whether the average actual duration most frequently matched, was longer than or shorter than the scheduled duration for each therapy. If the averaged actual duration of therapy was longer or shorter than the scheduled duration for a specific therapy, then changes were proposed to increase or decrease the scheduled duration, respectively. Proposed schedule lengths were rounded up to the next half-hour interval. The exception was if the next half-hour interval was less than 10 minutes from the average; an additional half-hour interval to the proposed appointment duration was added.

Development of Infusion Nurse Productivity Scorecard

Data from the in-person and electronic time studies were used to develop and validate metrics and metric parameters for the infusion nurse productivity scorecard (Table 3). The productivity scorecard comprised specific infusion therapies, ancillary tasks, allotted points to each therapy or ancillary task, and goal number of points for infusion nurses to achieve daily. Testing of the scorecard via retrospective grading of the time studies using the scorecard determined 15 points as the daily goal for a nurse to be considered "productive."

Discussion

In-Person Time Study

The in-person time study demonstrated not only the great number of tasks that infusion nurses performed throughout the day, but also the variety in tasks performed. It is interesting to note that nurses spent roughly equal percentages of time in all categories (except for tasks in the Other category), as opposed to predominantly spending their time in 1 or 2 categories (Figure 2). Additionally, it is interesting to note that the 2 categories in which nurses spent the most time (Indirect Patient Care and Documentation) were not categories that involved direct interaction with patients. It was helpful for the in-person time study to

FIGURE 2 | Breakdown of Infusion Nurse Time

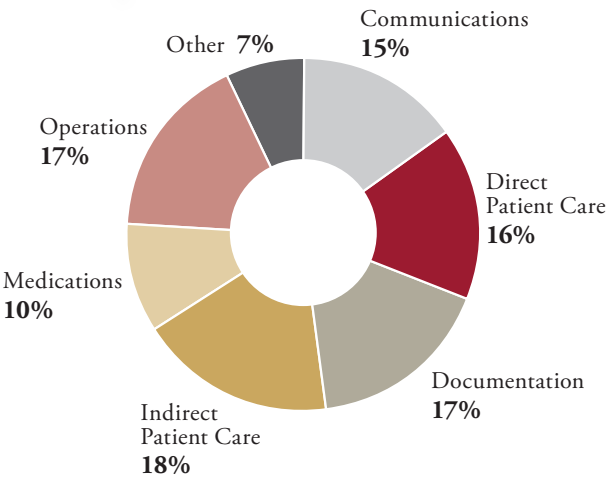

TABLE 2 | Infusion Therapies Given and Appointment Lengths [during May 2022 at 3 AIS sites (N=407)]

Therapy (n)	Brand[a]	Appointment Length(s) (min)	Averaged Actual Length (min)	Proposed Length (min)
Abatacept (4)	ORENCIA®	60, 90	75	90
Aripiprazole (1)	ABILIFY MAINTENA®	30	35	60 *[increase]*
Belatacept (1)	NULOJIX®	60	49	60
Belimumab (2)	BENLYSTA	120, 180	150	180
Cabotegravir/rilpivirine (2)	CABENUVA	60	68	90 *[increase]*
Eptinezumab-jjmr (10)	VYEPTI®	60, 90, 180	63	90
Golimumab (1)	SIMPONI ARIA®	90	74	90
Hydration (30)	n/a	90, 120	80	90
Infliximab (12) Infliximab-abda (12) Infliximab-dyyb (4)	REMICADE® RENFLEXIS® Inflectra®	190, 180, 210	153	180
Iron dextran (1)	INFeD®	210	251	270 *[increase]*
Iron sucrose (2)	Venofer®	60	52	90 *[increase]*
IVIg (11) IVIg (7) IVIg (7)	GAMMAGARD LIQUID GAMUNEX®-C Privigen®	180, 210, 240, 300, 360	248	270
Mepolizumab (9)	NUCALA	30, 60, 90	61	90
Natalizumab (102)	TYSABRI®	90, 120, 150, 180	134	150 (180 with premeds)
Ocrelizumab–Traditional Infusion (36)	OCREVUS®	150, 360, 480	368	390 (established visit) 480 (new visit)
Ocrelizumab–Shorter Infusion (1)	OCREVUS®	480	275	300 (established visit) *[decrease]* 480 (new visit)
Octreotide acetate (1)	SANDOSTATIN® LAR DEPOT	30	38	60 *[increase]*
Omalizumab (22)	XOLAIR®	30, 60, 90	61	90 (120 with premeds)
Patisiran (30)	ONPATTRO®	210, 240	199	210
Ravulizumab-cwvz (1)	ULTOMIRIS®	60	63	90 *[increase]*
Risperidone (3)	RISPERDAL CONSTA®	60	27	60
Rituximab (21) Rituximab-abbs (15)	RITUXAN® TRUXIMA®	480	285	300 (established visit) *[decrease]* 480 (new visit)
Sodium ferric gluconate complex (2)	Ferrlecit®	120	52	90 *[decrease]*
Tezepelumab-ekko (1)	TEZSPIRE®	30	29	60 *[increase]*
Tixagevimab/cilgavimab (11)	Evusheld™	90	112	150 *[increase]*
Ustekinumab (1)	STELARA®	120	92	120
VAD Care (21)	n/a	30	26	60 *[increase]*
Vedolizumab (2)	ENTYVIO®	90	53	90
Zoledronic acid (21)	Reclast®	90	112	150 *[increase]*

Abbreviations: IVIg = intravenous immunoglobulin; VAD = vascular access device, n/a = not applicable

[a] Specific brand name of medication administered if applicable.

paint a more complete, and complex, picture of what was being done to care for patients during infusion appointments, which was a picture that chair capacity did not necessarily depict.

It is worth noting that nurses were frequently found multitasking during observation. If a nurse was observed to be performing 2 tasks at the same time, the observed "primary action" (i.e., task perceived to be started first) was documented and time logged, with a note stating what the secondary action was. The in-person time study strived to accurately document when each task was started and stopped, even if an infusion nurse rapidly switched between 2 tasks. However, the time study results did not necessarily capture the mental load involved when infusion nurses balanced multiple patients and associated responsibilities all at the same time. Thus, it is worth considering the larger implications of multitasking on productivity, patient safety, and infusion nurse mental and emotional capacity.

Another interesting finding was the relatively smaller amount of time observed that nurses spent taking breaks. At our organization, full-time employees are expected to take a 30-minute lunch and may take two 15-minute breaks with the expectation that they would not be completed work-related duties. The total 60 minutes account for about 12% of a full workday. However, infusion nurses were observed to spend only 7% of their time in the day taking breaks. All but 1 nurse was observed not to take a formal lunch break. When asked why they did not step away for lunch, nurses stated they preferred to keep an eye on patients while eating in case they needed anything. While the nurses' commitment to their patients is commendable, this raises the question of how nurses can balance their commitment while also caring for themselves to prevent burnout.

The in-person time study was highly insightful, but it does present some limitations. One limitation was that only 7 infusion nurses were observed. Additionally, not all nurses were observed for an entire workday (e.g., 8.5 hours); some were observed for a full day, and others were observed for a half day. The results of the time study may present differently if more nurses were observed, or if all 7 nurses were observed for a full day each, or both. However, it is also possible that these factors may not affect the results since it is generally assumed that all nurses perform to similar degrees in terms of speed and skill.

Electronic Time Study

The intent of the electronic time study was to gain additional insight on how infusion nurses' time could be optimized. Historically, scheduling infusion appointments had been based on how long the infusion would be expected to take, with an additional 30 minutes added if the patient needed premeds before the infusion, as well as a 30-minute "buffer time" in between patient appointments. It was not necessarily expected that there would be many, if any, differences between the scheduled and actual appointment lengths when analyzing data from the electronic time study. However, it was interesting to note the differences that came up.

First, it was noted that a specific therapy may have been scheduled for a certain amount of time for 1 patient, but the same therapy was scheduled for a different amount of time for another patient, even if they had the same regimen. It was not explored in depth why these scheduled durations differed (e.g., patient-specific request to schedule a shorter infusion because they did not need an additional half hour for premeds). A contributing factor may be human-error-related drift away from standardization of scheduling patients for specific therapies. There may be a need to periodically audit appointment lengths to ensure that scheduling is streamlined and consistent. Additionally, following a standard operating procedure (e.g., clear indication of patient needed premeds; patient-specific infusion rates and durations) may help standardize those efforts.

Second, of the 34 infusion and injection therapies analyzed in the electronic time study, about one-third of the therapies presented differences between the scheduled and actual appointment duration large enough to warrant a proposed change in therapy duration. Specifically, it was proposed to increase the appointment length for 10 therapies and decrease the length for 3 therapies. There are several possible explanations for why several therapies may require a longer-than-expected appointment length. One may be due to the nature of the reconstitution and dilution process of certain therapies, especially those that take considerable time to dissolve into solution, must not be shaken, or require a separate filtration process. Another may be due to the need to slow down infusion rates if a patient experiences any adverse effect (even mild ones), such as flushing of the face, nausea, or tickling in the back of the throat. Great caution is taken in AIS sites to prevent a full-blown

anaphylactic reaction, especially since adverse drug reactions (ADRs) can happen at any appointment at any time, even if it is a maintenance dose. A third possible explanation is that if infusion nurses are handling several patients at once, their multitasking may be slowing down their productivity, especially if a nurse is caring for several patients with complex therapies at the same time and several patients require tending to at similar time intervals. On the contrary, there are possible explanations for why some therapies need less time than expected. For example, perhaps the initial precaution to embed more time in case of patient ADRs was too great, especially if there was a lack of real-world patient data that said otherwise. Now that there is information that supports reducing infusion therapy length, perhaps anxieties surrounding infusion-related reactions for specific therapies can be eased.

Overall, the electronic time study demonstrated that the actual practice of preparing and administering infusion therapies does not always align with theoretical expectations. However, it is worth noting the limitations of the electronic time study. The electronic time study was only performed for infusion appointments completed over the course of 1 month. It is possible that a larger sample size of completed appointments may call for different suggestions on how long to schedule appointments for specific therapies. In addition, the electronic time study only investigated 34 types of infusion or injectable therapies as listed in Table 2. It would be interesting to compare the expected and actual durations of therapy of other medications that were not studied. It should also be noted that only completed infusion appointments were included in the electronic time study; cancelled, rescheduled, or incomplete appointments (e.g., patient left against medical advice) were not included. It would be interesting to investigate these outliers in connection to the type of therapy to see if any possible explanations could be drawn.

Infusion Nurse Productivity Scorecard

Both the in-person and electronic time studies provided a wealth of information on how infusion nurses spend their time at AIS sites. The challenge was to figure out how to synthesize the information into a tool that would reflect clinician-focused capacity. The intent of the productivity scorecard was to be comprehensive to reflect the breadth of work that infusion nurses perform yet remain operable so it would not be cumbersome to use.

It is worth pointing out that the scorecard in Table 3 both parallels the traditional concept of chair capacity and expands into the idea of clinician-focused capacity. The top section that lists the type of therapy and respective proposed scheduling length (deducted from the electronic time study) and points per appointment parallels the concept of chair capacity. Longer infusions—which would imply longer times of patients occupying infusion chairs—result in more points. According to this productivity scorecard, 1 point is equal to 1 hour of chair time. The ancillary tasks were synthesized from the in-person time study in discussion with infusion nurse staff. Points upon completion of the ancillary tasks were awarded based on the magnitude of impact the tasks had on AIS operations and patient care.

After the infusion nurse productivity scorecard was developed, the scorecard metrics and goal number of points were validated by retrospectively applying the scorecard on the in-person time studies and scoring the 7 full-time infusion nurses who were observed. Results from these scores were used to adjust the scorecard metrics and points so it could become a more accurate tool for future use.

This infusion nurse productivity scorecard based on the principles of clinician-focused capacity has wide-ranging implications. The purpose of having these ancillary tasks listed in their own section was to recognize that not every infusion appointment is the same. Some appointments may be more complex than others. An extreme example would be an anaphylactic reaction that may require several unanticipated hours of care provided by the infusion nurse that would otherwise be spent tending to other patients. However, we recognized that an infusion nurse should be rewarded for handling this unexpected situation, as opposed to being potentially penalized for meeting lower chair capacity requirements. The list of ancillary tasks also strived to account for the day-to-day variability in AIS site operations. For example, if an infusion nurse was somehow scheduled to see fewer patients than usual for a certain day, the nurse can remain productive by taking on additional ancillary tasks and assisting other nurses. Infusion nurses should not be put at a disadvantage for scheduling factors outside of their control. By focusing on what infusion nurses spend their time doing as opposed to only focusing on physical chair utilization, infusion nurses can be recognized for both the work they are assigned to do and what they do when going above and beyond their individually assigned duties.

TABLE 3 | Proposed AIS Infusion Nurse Productivity Scorecard

Therapy	Proposed Scheduling Length (min)	Points (per appt)
Abatacept (ORENCIA®)	90	1.5
Aripiprazole (ABILIFY MAINTENA®)	60	1
Belatacept (NULOJIX®)	60	1
Belimumab (BENLYSTA)	180	3
Cabotegravir/rilpivirine (CABENUVA)	90	1.5
Eptinezumab-jjmr (VYEPTI®)	90	1.5
Golimumab (SIMPONI ARIA®)	90	1.5
Hydration	90	1.5
Infliximab (REMICADE®)	180	3
Infliximab-abda (RENFLEXIS®)	180	3
Infliximab-dyyb (Inflectra®)	180	3
Iron dextran (INFeD®)	270	4.5
Iron sucrose (Venofer®)	90	1.5
IVIg (GAMMAGARD LIQUID)	270	4.5
IVIg (GAMUNEX®-C)	270	4.5
IVIg (Privigen®)	270	4.5
Mepolizumab (NUCALA)	90	1.5
Natalizumab (TYSABRI®)**	150	2.5
Ocrelizumab (OCREVUS®)—Traditional Infusion	390	6.5
Ocrelizumab (OCREVUS®)—Shorter Infusion	300	5
Octreotide acetate (SANDOSTATIN® LAR DEPOT)	60	1
Omalizumab (XOLAIR®)**	90	1.5
Patisiran (ONPATTRO®)	210	3.5
Ravulizumab-cwvz (ULTOMIRIS®)	90	1.5
Risperidone (RISPERDAL CONSTA®)	60	1
Rituximab (RITUXAN®)	300	5
Rituximab-abbs (TRUXIMA®)	300	5
Sodium ferric gluconate complex (Ferrlecit®)	90	1.5
Tezepelumab-ekko (TEZSPIRE®)	60	1
Tixagevimab/cilgavimab (Evusheld™)	150	2.5
Ustekinumab (STELARA®)	120	2
VAD Care	60	1
Vedolizumab (ENTYVIO®)	90	1.5
Zoledronic acid (Reclast®)	150	2

**Add 30 min (0.5 point) for premeds

Ancillary Tasks	Description	Points
Labs & paperwork	Drawing labs and completing paperwork	0.25 (per pt)
Labs drop off	Delivering lab samples to internal or external lab	0.25 (per run)
Mix medication	Reconstituting and diluting medication for infusion or injection	0.5 (per pt)
Organize delivery	Receiving and organizing medications for patients	0.5 (per day)
Scheduling	Scheduling patient appointments and emailing intake team	0.25 (per pt)
Call patient (e.g., conduct COVID-19 screen)	Calling patient to confirm appt and screening for COVID-19	0.5 (per day)
Chart checks (e.g., assess appointments 1-2 weeks out)	Reviewing patient chart for future orders and labs needed	0.5 (per day)
Patient teaching/ education	Counseling patient on treatment/line care	0.5 (per pt)
Help another nurse's patient	Helping nurse to e.g., insert IV, take vitals for another patient	0.25 (per pt)
Patient ADR & documentation	Stopping infusion and administering rescue medications and/or interventions	1 (per pt)
Patient troubleshooting	e.g., patient shows up but not on schedule	1 (per pt)
TOTAL SCORE (GOAL 15 POINTS)		

We recognize this scorecard also comes with some limitations. Notably, not every AIS site across different organizations may operate in the same fashion. It should be noted that while 15 points was considered "productive" for AIS infusion nurses at our organization, that number may look different at another organization, or even at another site within our organization that was not part of this study. We wish to disclose that this scorecard does not intend to establish a one-size-fits-all model to measure productivity at all AIS sites. It can be customized to better fit the specific operations at a particular AIS site, since not every site may operate in the same fashion. Another limitation is the assumption that all infusion nurses operate at the same speed and have the same expertise in skill. While we believe there is a standard of excellence to which all infusion nurses should be held, scoring an infusion nurse with no prior experience in infusion therapies would be an unfair comparison to scoring an infusion nurse with several years of experience. The intent of this scorecard was to align with AIS site management's general expectation of how an infusion nurse should perform, not necessarily be used as a tracker for onboarding new nurses.

Despite these limitations, we are hopeful that the infusion nurse scorecard can be implemented as a useful tool to measure AIS site productivity. We hope to pilot the rollout of the productivity scorecard in our organization's studied AIS sites. Application of the scorecard in day-to-day practice can help with refining appointment lengths, points, and productivity goals. Additionally, the scorecard can be expanded to include additional therapies as AIS sites expand their formularies. In the long term, this productivity scorecard has potential for adoption across all AIS sites after further tuning for operational differences at non-studied sites. There is also potential to identify comprehensive productivity metrics for other AIS personnel, such as pharmacists and medical assistants, like the metrics used to measure productivity for infusion nurses in this study.

Conclusion

The time studies performed in this research highlighted trends and potential areas of improvement in AIS nurse workflow, scheduling, and resources. The data and insights gathered from the time studies allowed for development of an operational scorecard that encompassed the spirit of clinician-focused capacity instead of chair capacity. The hope for the infusion nurse productivity scorecard is to help AIS management evaluate productivity more holistically during business performance reviews. Clinician-focused capacity has the potential to expand in scope to apply to other AIS site personnel and provide a more comprehensive picture of the all the work that infusion personnel put into providing high-quality care to patients at AIS sites.

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Cefazolin-Induced Neutropenia Development and Evaluation of Risk Factors in Home Infusion (CINDER-FHI)

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ABSTRACT

Background

Beta-lactam-induced neutropenia (BLIN) is a serious adverse reaction associated with extended treatment courses. For many severe infections, guideline-directed medical therapy frequently involves weeks or months of IV antibiotics. To avoid health care costs associated with hospitalization and as a method to improve hospital bed capacity, clinicians are encouraged to discharge patients to receive IV antibiotics in the ambulatory setting once clinically stable. The purpose of this study was to compare the incidence of cefazolin-induced neutropenia between intravenous push (IVP) administration and intermittent infusions among home infusion patients. This study is unique in its analysis of neutropenia monitoring and interventions in a pharmacist-led outpatient parenteral anti-infective therapy (OPAT) model. Cefazolin was examined over other beta-lactams due to high utilization in home infusion and administration methods by IVP and intermittent infusion at this institution.

Methods

This was a retrospective cohort study within a single large health system that includes an associated home infusion pharmacy. Patients were included for analysis if they met the following criteria: ≥18 years of age, received cefazolin through the home infusion pharmacy between July 1, 2017, and July 1, 2022, and were discharged from an acute care site within the health system for index cefazolin episode to the home or an affiliated long-term care facility. Lab values within 2 weeks of the cefazolin treatment course were evaluated for neutropenia. The primary outcome was the incidence of neutropenia by the method of administration: IVP versus intermittent infusion. Patients who received intermittent infusions in this study utilized elastomeric devices or ambulatory infusion pumps. Duration of IVP and intermittent infusion were defined as being given over 10 minutes and 30 minutes, respectively.

Results

A total of 431 patients were included in the study. Home infusion pharmacists recorded 18 BLIN events. All patients were asymptomatic. Fourteen events were classified as mild, with an absolute neutrophil count (ANC) nadir of 1.1-1.5 cells×1000/μL. Two events were considered moderate and 2 were considered severe, with ANC nadirs between 0.5 to 1.0 cells×10^3/μL and <0.5 cells×10^3/μL, respectively.

Conclusions

The relationship between baseline ANC and the development of BLIN later in treatment reported a 3.4-fold increased risk of cefazolin-induced neutropenia, and individuals with neutrophil counts between 1.6×10^3 cells/μL and 3.9×10^3 cells/μL at baseline require the highest degree of care. Our data suggests that low absolute neutrophil count (ANC) at cefazolin initiation is the strongest risk factor for subsequent development of neutropenia.

Keywords: beta-lactams, home infusion, neutropenia, intravenous push, infusion.

Background

Beta-lactam-induced neutropenia (BLIN) is a serious adverse reaction associated with extended treatment courses. It is characterized by decreased levels of neutrophils, often defined as absolute neutrophil count (ANC) ≤1.5 with at least 10-12 days of beta-lactam therapy.[1,2] Numerous proposed mechanisms exist, including immune-mediated hypersensitivity reaction, direct cellular toxicity, and suppressed humoral immunity.[3-5] For cephalosporins, the prevailing theory involves the formation of haptens (protein adducts) with neutrophils, which prompts an immune response, resulting in neutropenia, particularly with durations of therapy exceeding 2 weeks.[6-10] Modifications of the cephalosporin chemical structure occur at R sites on the core beta-lactam ring and differentiate the spectrum of activity. Both R1 and R2 side chains on the beta-lactam ring have been implicated in the process of immune recognition.[10,11] Suggested risk factors for BLIN include increased cumulative exposure and prolonged treatment durations.[11] One recent study showed a correlation between cefepime-induced neutropenia and intravenous push administration, and another study of hospitalized pediatric patients found younger age was associated with neutropenia development.[12,13] Incidence of BLIN varies based on the beta-lactam utilized and the total duration of therapy. Approximate incidence based on duration of therapy greater than 2 weeks is 10%.[11]

For many severe infections, such as osteomyelitis, endocarditis, and bacteremia, guideline-directed medical therapy frequently involves extended courses of IV antibiotics.[11,14] To avoid health care costs associated with extended hospitalization and as a method to improve hospital bed capacity, clinicians are encouraged to discharge patients to receive IV antibiotics in the ambulatory setting once clinically stable. Home infusion represents a rapidly growing industry where patients can receive IV antibiotics safely, effectively, and conveniently in their homes.[15] Due to decreased costs and patient convenience, home infusion has become the standard of care for outpatient parenteral antibiotic therapy (OPAT).[11,15]

Several methods of medication administration seen in home infusion are intravenous push (IVP), elastomeric devices, dial-regulated gravity infusions, and ambulatory pumps.[16] Many patients prefer IVP because of its ease of use. Once connected to the patient's indwelling line, IVP is usually given over 2-10 minutes, depending on the medication. Elastomeric devices are available in a variety of administration rates and can be used for short intermittent infusions as well as extended continuous infusions of 3 hours or more. Ambulatory pumps are programmed for the prescribed administration rate and can be used for short infusions or extended infusions. Infusion duration and frequency of drug administrations are important considerations when selecting between administration methods. The efficacy of cephalosporin antibiotics is dependent upon maximizing the duration of time that drug concentrations remain above the minimum inhibitory concentration (MIC) of the target pathogen.[17] Data shows that either IVP or intermittent infusion are appropriate for cephalosporin administration.[17]

Cefazolin is commonly dosed 3 times daily, and it is a good candidate to be administered via IVP in the home, although it may also be given via an elastomeric device or ambulatory pump. Cefazolin covers *Streptococci*, methicillin-susceptible *Staphylococci* (MSSA), and some Gram-negative organisms. It also has enhanced patient convenience compared to penicillinase-resistant semisynthetic penicillins such as nafcillin and oxacillin, which are dosed every 4-6 hours or as a continuous infusion, necessitating more frequent administrations or attention to the administration device.[18] These factors have quickly made cefazolin a drug of choice in home infusion for management of bloodstream infections, endocarditis, and bone or joint infections, especially those due to MSSA.

The aim of this study was to compare the incidence of cefazolin-induced neutropenia between IVP and intermittent administration among home infusion patients. The secondary outcome of the study was to explore additional risk factors for cefazolin-induced neutropenia. Herein we address a gap of evidence evaluating risk factors for BLIN in the home infusion setting. This study is also unique in its analysis of neutropenia monitoring and interventions in a pharmacist-led OPAT model. Cefazolin was examined over other beta-lactams due to high utilization in home infusion and adequate administration by both IVP and intermittent infusion at this institution.

Methods

Study Setting and Population.

This was a retrospective cohort study within a single large health system that includes an associated home infusion company. Patients were included for analysis if they met the following criteria: ≥18 years of age, received cefazolin through the home infusion pharmacy between July 1, 2017, and July 1, 2022 and were discharged from an acute care site within the health system for index cefazolin episode to the home or an affiliated long-term care facility. Race was self-reported and extracted from the electronic medical record. Similarly, the total duration of therapy was identified via addition of both inpatient and outpatient antibiotic course durations via electronic medical record. Patients without a documented stop date were defined as having an indeterminate treatment duration. Patients were excluded if they had neutropenia at baseline prior to OPAT, a history of any chemotherapy or bone marrow transplantation within 90 days prior to or during cefazolin treatment or had inadequate lab data to assess for neutropenia throughout treatment. The University of Minnesota institutional review board (IRB) approved this study.

ANC at cefazolin initiation was interpreted as being on the low end of normal for values 1.6-3.9 cells×1000/μL. ANC values 4.0-6.9 cells×1000/μL were considered normal. ANC greater than 7.0 cells×1000/μL was considered elevated. All lab values within 2 weeks of the cefazolin treatment course were evaluated for neutropenia, defined as ANC ≤1.5 and further classified into one of several categories. Mild, moderate, and severe neutropenia were defined as 1.5-1.0, <1.0-0.5, and <0.5 cells×1000/μL, respectively. For logistic regression analysis, patients were categorized into groups based on age, ANC, and duration of treatment to determine whether these factors impact the incidence of BLIN. Grouping criteria seen in Table 4 were selected by investigator choice a priori. Reference ranges were selected as comparators based on the hypotheses that incidence of neutropenia would increase with older age, longer treatment durations, and decreased baseline ANC. Upon identification of cefazolin-induced neutropenia, a chart review was conducted to identify management strategies and assess for potential symptomatic neutropenia, characterized by new fevers or new or worsening infection.

Data Collection and Variables of Interest

Study data were collected and managed using the Research Electronic Data Capture (REDCap®). Patient race, sex, age, research authorizations, hospital admission discharge dates, and method of administration were retrieved via pharmacy analytics report. Manual chart review was conducted to confirm and document laboratory data and duration of cefazolin treatment. Chart reviews were conducted independently by 2 investigators. Upon identification of neutropenic events, pharmacist and provider interventions were assessed. Any discrepancies were resolved via discussion and consensus with a third pharmacist within the research team.

The primary outcome was incidence of neutropenia by method of administration: IVP versus intermittent infusion. Patients who received intermittent infusions in this study utilized elastomeric devices or ambulatory infusion pumps. Duration of IVP and intermittent infusion was defined as being given over 10 minutes and 30 minutes, respectively. As a secondary outcome, the following covariates were analyzed for correlations with incidence of neutropenia: duration of OPAT, sex, age, race, and baseline ANC.

Statistical Analysis

The distribution of continuous variables was examined for normality. Categorical variables were compared with neutropenia status using chi-squared tests. Univariate logistic regression models estimated the odds of becoming neutropenic by each variable of interest, with 95% confidence intervals reported. Statistical significance was determined a priori at $\alpha=0.05$ for all comparisons. All analyses were conducted in SAS®, version 9.4 (SAS®, Inc., Cary, NC).

Results

A total of 431 patients were included in the study. Baseline characteristics are listed in Table 1 by the characteristic variable, and by infusion method of either infusion (30 minutes) or IV push (10 minutes).

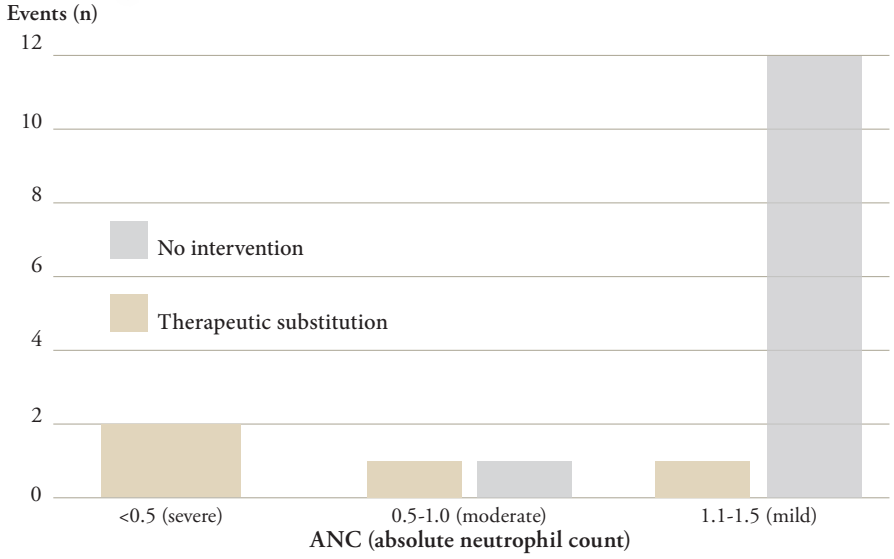
Home infusion pharmacists recorded 18 BLIN events as visualized in Figure 1. In each scenario, home infusion pharmacists notified providers of neutropenic events and engaged in shared decision-making. All patients were asymptomatic. Fourteen events were classified as mild, with an ANC nadir

TABLE 1 | Baseline and Descriptive Characteristics

Characteristic	Infusion n= 80 (%)	IV Push n=351 (%)	Total n=431 (%)
Male sex	39 (48.8)	210 (59.8)	249 (57.8)
Female sex	41 (51.2)	141 (40.2)	182 (42.2)
Age, years; mean (std dev)	72 (11.8)	54 (14.9)	57 (16.1)
18-49, years	4 (5.0)	130 (37.0)	134 (31.1)
50-64, years	16 (20.0)	151 (43.0)	167 (38.7)
65+, years	60 (75.0)	70 (20.0)	130 (30.2)
Race			
White	70 (87.5)	298 (84.9)	368 (85.4)
Black or African American	2 (2.5)	22 (6.3)	24 (5.6)
Asian	1 (1.3)	15 (4.3)	16 (3.7)
Undisclosed	4 (5.0)	11 (3.1)	15 (3.5)
Other	3 (3.7)	5 (1.4)	8 (1.8)
Baseline ANC, ×103 cells/μL; median (IQR)	8.0 (7.5)	7.3 (6.9)	7.4 (6.9)
Low: 1.6-3.9 cells×1000/μL	10 (12.5)	52 (14.8)	62 (14.4)
Normal: 4-6.9 cells×1000/μL	20 (25.0)	110 (31.3)	130 (30.2)
Elevated: >7 cells×1000/μL	50 (62.5)	189 (53.8)	239 (55.5)
ANC reduction, cells ×1000 /μL; median (IQR)	4.3 (5.1)	3.3 (5.8)	3.3 (5.7)
OPAT Duration, days; median (IQR)	36 (16.0)	28 (22.0)	29 (21.0)
0-4 weeks	22 (27.5)	158 (45.0)	180 (41.8)
4-6 weeks	25 (31.2)	83 (23.6)	108 (25.1)
>6 weeks	20 (25.0)	64 (18.2)	84 (19.5)
Indeterminate	13 (16.3)	46 (13.1)	59 (13.6)

Std dev= standard deviation; IQR= interquartile range

FIGURE 1 | Management of Neutropenia by Neutropenic Event Severity (n=18)



X axis = ANC nadir given in cells×103/μL (interpretation). Y axis = incidence of event.

of 1.1-1.5 cells×1000/μL. Two events were considered moderate and 2 were considered severe, with ANC nadirs between 0.5-1.0 cells×10^3/μL and <0.5 cells×10^3/μL, respectively. Figure 1 shows that 14% of all mild events led to an intervention compared to 50% of moderate events and 100% of severe events. When therapeutic substitution was considered necessary per prescriber discretion, new antibiotic therapy was restarted as soon as feasible. This strategy was effective, as patient ANC counts spontaneously recovered without any additional intervention. Across all neutropenic events, the mean time to recovery was 9.1 days (range 1-28 days). Two neutropenic events occurred at the end of therapy, where no lab data was available to assess neutrophil recovery after discontinuation.

The primary outcome of neutropenia incidence by administration type did not generate statistically significant results, as seen in Table 2. These results are contrary to previous studies demonstrating higher rates of neutropenia with more rapid IVP administration of beta-lactams.[12]

TABLE 2 | Primary Outcome: Neutropenia Incidence by Administration Type

Administration Type	Neutropenic Events	Incidence	*p*-Value
Infusion	4/80	5.0%	0.683
IV Push	14/351	4.0%	

Additional covariates were analyzed for correlations with incidence of BLIN in Table 3 and Table 4, including sex, race, baseline ANC, treatment duration, and patient age. Sex, race, treatment duration, and patient age demonstrated no statistically significant correlation with BLIN incidence. In addition, having a low baseline ANC (1.6-3.9×10^3 cells/μL) was the covariate that was most closely correlated with development of BLIN later in treatment and was statistically significant (OR 3.41; 95% CI 1.03 – 11.28).

Discussion

In this retrospective cohort study of patients receiving OPAT with cefazolin, baseline ANC was the greatest predictor for risk of neutropenic events. Patients with a baseline ANC between 1.6 and 3.9 were roughly 3.4 times more likely to experience a neutropenic event. In contrast to previous studies, no statistically significant differences in the incidence of neutropenia based on the method of delivery (IV push vs. intermittent infusion) were observed.

This study represents important progress for OPAT in home infusion. In the context of acute infection, neutrophil counts generally remain within normal ranges. Low neutrophil levels can indicate an underlying condition predisposing the patient to future neutropenic events. All events observed in this study were asymptomatic, and most were mild (ANC 1.5-1.1), requiring no intervention. Key cutoffs for neutropenia necessitating intervention are not well established and may be patient specific. Pharmacists play a critical role in monitoring labs, assessing risk for neutropenia, and relaying concerns to providers. Out of 18 incidents of BLIN, 5 led to an intervention. The pharmacist was responsible for monitoring for BLIN and reporting patient lab results to the prescriber. In conjunction with the prescriber, the pharmacist coordinated medication interventions. This finding supports the safe and effective practice of a pharmacist-led home infusion service for monitoring response to treatment in OPAT.

While a past medical history of antibiotic allergy was not included in the statistical analysis, investigators observed little correlation between allergy history and neutropenic events. If an immunologic mechanism is responsible for cefazolin-induced neutropenia, one might expect a prior antibiotic allergy to be a predisposing factor in the risk of developing antibiotic-induced neutropenia, particularly if the allergy were to a cephalosporin. This correlation was not observed, and since immune recognition has been associated with variations in R side chains of the beta-lactam ring, the research acknowledged that cefazolin does not share any similar or identified R1 or R2 side chains with other beta-lactams.

This study has several limitations. BLIN is rare and multifactorial; establishing a correlation with any 1 covariate is challenging. Thus, this study was underpowered to detect statistically significant differences in several key metrics. Statistically nonsignificant primary outcome results may be due to several factors. Patient preference for IVP administration makes adequately powering an IV infusion group challenging. Furthermore, age distributions between IVP and infusion groups

TABLE 3 | Incidence of BLIN Based on Sex and Race

Characteristics		Neutropenic Events	Incidence	*p*-Value
Sex	Female	8/180	4.4%	0.827
	Male	10/249	4.0%	
Race	White	15/368	4.1%	0.913
	African American	1/24	4.2%	
	Asian	1/16	6.3%	

TABLE 4 | Risk of BLIN Based on Age, Baseline ANC, and Cefazolin Duration

Characteristics		Neutropenic Events	Incidence	OR (95% CI)
Age (years)	18-49	6/134	4.5%	*reference*
	50-64	7/167	4.2%	0.96 (0.31, 2.93)
	65+	5/130	3.8%	0.89 (0.27, 3.01)
Baseline ANC (cells×1000/μL)	Low: 1.6-3.9	7/62	11.3%	3.41 (1.03, 11.28)
	Normal: 4-6.9	5/130	3.8%	*reference*
	Elevated: ≥7	6/239	2.5%	0.65 (0.19, 2.18)
Cefazolin duration (weeks)	0-4	5/180	2.8%	*reference*
	4-6	7/108	6.5%	2.51 (0.78, 8.11)
	>6	6/84	7.1%	2.81 (0.83, 9.47)

OR= odds ratio; CI= confidence interval; ANC= absolute neutrophil count. Patients were excluded from this analysis if total duration of cefazolin treatment was indeterminate.

must be considered. Generally, both geriatric and pediatric populations are more susceptible to adverse effects.[19] This has been seen with BLIN, specifically in pediatric patients; although, as of now, no study has been identified showing older age to be associated with BLIN.[13] Still, the potential for confounding with distributions of geriatric patients differing between groups (75% vs. 20%) must be considered.

Additionally, patients in the IVP group were educated to administer cefazolin over 10 minutes, on the conservative end of the IVP administration range. A recent study associated rapid IV push of cefepime with the rate of infusion administered IVP mediation over 3-5 minutes.12 The conservative approach for IVP administration in this study may indicate that a slower administration rate for IVP medications may mitigate the adverse effect. Furthermore, generalizability of these results to other sites may be limited by the observed patient characteristics. Overall, 85.4% of patients in this study were self-reported as white race. Thus, these results may translate differently to more racially diverse patient populations.

Neutropenic events increase in frequency with increasing antibiotic durations. In most cases, neutropenic events occurred at or near the end of therapy. As a result, therapy was discontinued as planned, and ANC was rechecked at the follow-up appointment to confirm resolution, often 1-2 weeks later. However, ANC may have recovered well before the follow-up level was drawn. As a result, data on the duration of neutropenia was imprecise. Documentation of antibiotic stop dates for patients transferred to affiliated long-term care facilities was often not well documented within electronic health records. While these patients were not excluded from the study, they could not be included in logistic regression analysis without an appropriate duration of therapy.

Other covariates will be reassessed for correlations with BLIN in a follow-up study. Duration of treatment was of particular interest. Despite being underpowered to detect statistical differences, we observed odds ratios of 2.5 and 2.8 for durations of 4-6 weeks and 7+ weeks, respectively. If these results hold up to a larger sample size, this will confirm

previous literature identifying longer treatment durations as a significant risk factor for BLIN. Notably, this study excluded patients with baseline ANCs below 1.5×10^3 cells/μL. Thus, additional studies are necessary to address optimal OPAT management for patients with baseline neutropenia or those receiving myelosuppressive chemotherapy.

Current recommendations for the management of BLIN are nonspecific and leave much to provider assessment based on ANC cutoffs and current risk of decompensation. Management strategies often start with careful laboratory monitoring in long-term beta-lactam treatment courses. In mild and asymptomatic BLIN, discontinuation of the offending agent is not always necessary. Watchful waiting and more frequent monitoring may prevent further decompensation. For patients at higher risk, transitioning to a beta-lactam containing an alternative R1 side chain is common. Finally, providers may utilize G-CSF to bolster the immune system and minimize infection risk; however, this was not observed in our study and is typically reserved for severe symptomatic neutropenia.[11] Future development of a management algorithm for BLIN may hasten the continued success of OPAT in a home infusion setting.

Conclusions

The primary takeaway from this study is the relationship between baseline ANC and the development of BLIN later in treatment. With a 3.4-fold increased risk of cefazolin-induced neutropenia, individuals with neutrophil counts between 1.6×10^3 cells/μL and 3.9×10^3 cells/μL at baseline require the highest degree of care. Based on these results, we recommend these patients get a baseline ANC measurement during the inpatient period and a thorough screening to identify other possible sources of neutropenia. Once discharged to home infusion, laboratory monitoring should be continued for cefazolin courses with durations greater than 2 weeks. Secondarily, this study provides valuable insight into neutropenia monitoring and interventions in a pharmacist-led OPAT model.

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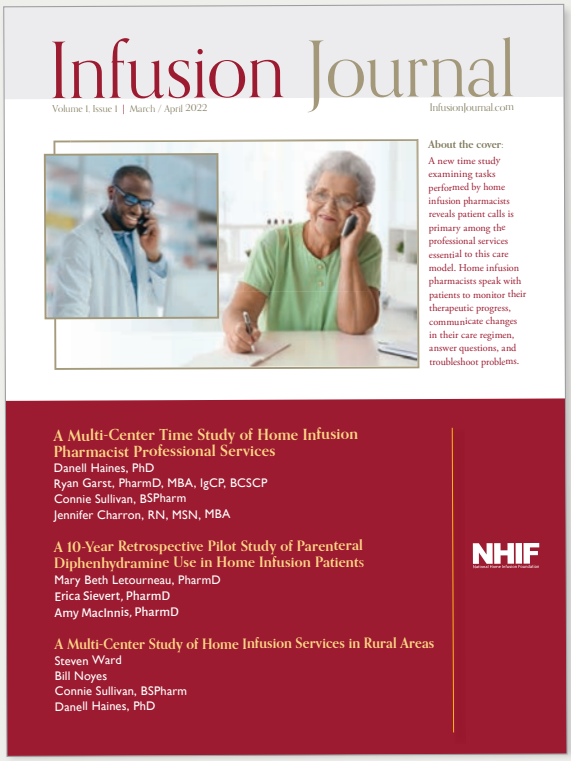

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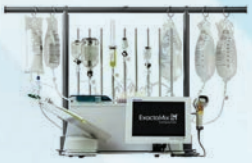

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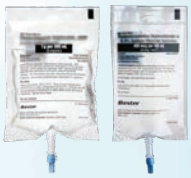

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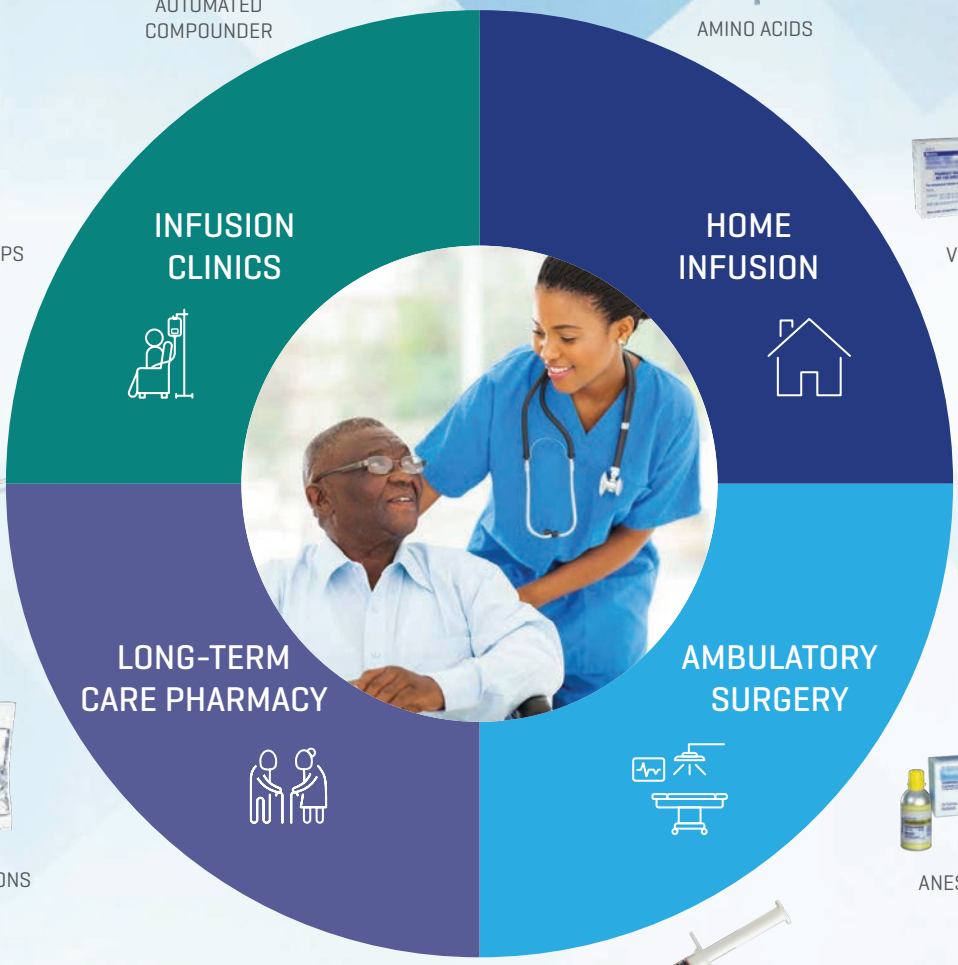

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