Development and Evaluation of an Intravenous Infusion Sequence Annotation System

Ji Qiu[1] Tingting Deng[2] Zhuo Wang[3] Zhangwei Yang[4] Ting Liu[1] Yunjie Liu[1] Rui Li[1] Fu Dai[5]

[1] Department of Pharmacy, Hefei Binhu Hospital, Hefei, Anhui, China
[2] Sichuan Kelun Pharmaceutical Co., Ltd, Chengdu, Sichuan, China
[3] Department of Pharmacy, Shanghai Changhai Hospital, Shanghai, China
[4] Information Section, Shanghai Fourth People's Hospital, Shanghai, China
[5] Hefei Binhu Hospital, Hefei, Anhui, China

Address for correspondence Fu Dai, PhD, Hefei Binhu Hospital, Hefei, Anhui 230000, China (e-mail: hfsyy123@163.com).

Appl Clin Inform 2021;12:65–72.

Abstract

Objectives The sequence of intravenous infusions may impact the efficacy, safety, and cost of intravenous medications. The study describes and assesses a computerized clinical decision support annotation system capable of analyzing the sequence of intravenous infusions.

Methods All intravenous medications on the hospital formulary were analyzed based on factors that impact intravenous infusion sequence. Eight pharmacy infusion knowledge databases were constructed based on Hospital Infusion Standards. These databases were incorporated into the computerized sequence annotation module within the electronic health record system. The annotation process was changed from pharmacists' manual annotation (phase 1) to computer-aided pharmacist manual annotation (phase 2) to automated computer annotation (phase 3).

Results Comparing phase 2 to phase 1, there were significant differences in sequence annotation with regards to the percentage of hospital wards annotated (100% vs. 4.65%, chi-square $= 180.95$, $p < 0.001$), percentage of patients annotated (64.18% vs. 0.52%, chi-square $= 90.46$, $p < 0.001$), percentage of intravenous orders annotated (75.67% vs. 0.77%, chi-square $= 118.78$, $p < 0.001$), and the number of tubing flushes per ward per day (118.51 vs. 2,115.00, $p < 0.001$). Compared with phase 1, there were significant cost savings in tubing flushes in phase 2 and phase 3. Compared with phase 1, there was significant difference in the time nurses spent on tubing flushes in phase 2 and phase 3 (1,244.94 vs. 21,684.8 minutes, $p < 0.001$; 1,369.51 vs. 21,684.8 minutes, $p < 0.001$). Compared with phase 1, significantly less time was required for pharmacist annotation in phase 2 and phase 3 (90.6 vs. 4,753.57 minutes, $p < 0.001$; 0.05 vs. 4,753.57 minutes, $p < 0.001$).

Conclusion A computerized infusion annotation system is efficient in sequence annotation and significant savings in tubing flushes can be achieved as a result.

Keywords
- pharmacy
- pharmacy information systems
- computer-assisted decision-making
- knowledge modeling and representation
- safety

received
August 22, 2020
accepted after revision
December 9, 2020

DOI https://doi.org/10.1055/s-0041-1722871.
ISSN 1869-0327.

Background and Significance

Patients often receive medications that are administered via intravenous infusion route during hospitalization, for example, approximately 90% of patients receive intravenous medications in Chinese hospitals.[1,2] Intravenous medications are associated with the highest risk of medication errors which can arise at any point in the medication use process from compounding to medication administration.[3] To ensure safety and efficacy, intravenous admixtures are usually compounded by hospital Pharmacy Intravenous Admixture Services (PIVAS) after prescription orders are reviewed and verified by PIVAS pharmacists. Intravenous order reviews focus on identifying inappropriate orders, such as indication for use, contraindications to therapy, diluent choice, volume of diluent, and coadministration of incompatible medications.[1] Once intravenous bags are compounded, they are sorted, and then batch delivered to hospital wards for nursing administration.

Commonly, a hospitalized patient may receive multiple intravenous infusions throughout the day, an average of four to five intravenous bags per patient per day in Chinese hospitals.[4] In Chinese hospitals, intravenous medications are commonly prescribed and administered based on default administration times, for example, 0800 for once-daily medications or 0800 and 1600 for twice-daily medications. Patients may have more than one intravenous to be administered at these default times. When certain medications are not given in a particular sequence, administration complications may occur, such as physical property changes, including turbidity, precipitation, or discoloration. The pharmacokinetic and pharmacodynamic properties of the medications may also be altered.[5] Flushing of tubing devices are often required if two incompatible infusions are administered sequentially.[6] These potential administration sequence complications may impact the safety and effectiveness of intravenous medications.[7]

Multiple factors are considered to determine infusion sequences for intravenous medications, including: (1) the stability of intravenous admixtures (intravenous medications need to be administered prior to their beyond-use-dates [BUDs] once compounded), (2) incompatibilities between sequentially infused medications (turbidity, discoloration, and precipitation may occur when incompatible intravenous infusions are not separated or tubing is not flushed in-between infusions), (3) premedications that should be infused before chemotherapy drugs to prevent or reduce the toxicities of chemotherapy (prevention drugs before treatment drugs), (4) the infusion of vesicants, as vesicants should be administered first since veins will not be irritated by other agents and because postvesicant flushing will preserve integrity of the veins,[8] (5) improved patient safety and efficacy with an emphasis on chronopharmacology,[9] and (6) sequence-dependent antitumor drugs, as the order of administration may dictate whether a particular effect or side effect is encountered based on the pharmacokinetics and pharmacodynamics of the medication. For example, when cisplatin is given before paclitaxel, profound and prolonged neutropenia may occur. This can delay the patient from receiving chemotherapy as prescribed. However, when the sequence is reversed, this detrimental side effect is diminished, and the therapy remains efficacious.[7]

In recent years, hospitals have developed technological platforms to address issues regarding the rational, safe, and effective use of intravenous infusions. An integrated "medicine–pharmacy–nursing" Intravenous Prescription Early Warning and Assessment System (IPEWAS) was constructed at Xiangya Hospital of Central South University in China.[10] The IPEWAS provides real-time clinical decision support (CDS) to physicians, pharmacists, and nurses regarding intravenous prescriptions, order review/verification, and appropriate infusion administration. The IPEWAS has made positive impacts on the rational administration of intravenous infusions.[10] Additionally, a new drip infusion solution monitoring system has been developed for use in hospitals and other care facilities. The system closely monitors the drip rates of intravenous infusions of several patients at nurses' stations.[11,12]

Providing the annotation of patient's intravenous infusion sequences to guide nursing administration is an extension of the PIVAS service. This service improves the prospective order review process, as well as the compounding process, to ensure the safe and effective administration of compounded intravenous medications. This process can be achieved either by manual annotation based on individual pharmacist's clinical knowledge and drug information resources or by automated computer annotation with the incorporation of CDS databases. Given the large number of intravenous bags administered at hospitals and the constant changes of medication orders for a patient, a PIVAS CDS Sequence Annotation (PCSA) system was implemented.

Objectives

The current study was conducted to evaluate the impact of a PCSA system. The following outcomes were assessed: (1) improvement of work efficiencies for pharmacists and nurses, (2) reduction in health care costs from fewer infusion tubing flushes, and (3) enhancement of infusion safety. The following indicators were analyzed concerning the outcome of the PCSA system: (1) utility indicators, such as the percentages of infusion sequences annotated with regards to hospital wards, patients, and intravenous medication orders, the numbers of intravenous tubing flushes (times/day), and the cost of intravenous tubing flushes (the US dollar, USD/year), (2) work efficiency indicators, including pharmacist time spent on annotation (minutes/day) and nursing time spent on flushing tubes (minutes/day), and (3) infusion safety indicators, including the number of bags with property changes within the infusion tubing, and the number of bags with property changes outside the infusion tubing. The study was considered to be an Exempt Research by the Hospital Ethics Committee.

Methods

Data Sources

The study was conducted at Hefei Binhu Hospital, a 1,500-bed tertiary hospital in Anhui Province, China. Intravenous bags are compounded at the hospital PIVAS center and delivered

three to four times a day in batches at scheduled times. The study period was from January 1, 2017 to September 30, 2019 and included three phases. During phase 1 (the control group, conducted January 1, 2017 to September 30, 2017), infusion manual sequence annotation was performed by PIVAS pharmacists with no CDS support before the implementation of the PCSA system. Pharmacists relied on clinical knowledge, the Hospital Infusion Standards, and drug information resources to annotate infusion sequences. During phase 2 (conducted January 1, 2018 to September 30, 2018), computer-aided manual sequence annotation was performed by PIVAS pharmacists. Eight infusion drug databases were established based on the Hospital Infusion Standards and were later incorporated into the PIVAS system. The PIVAS system displayed appropriate infusion sequences to facilitate pharmacists' manual annotation. Although this process was a considerable advancement over phase 1, the process still was not automated. During phase 3 (conducted January 1, 2019 to September 30, 2019), automated infusion sequence annotation was performed by the PCSA system.

Data Collection

Prior to the development of the PCSA system, the Hospital Infusion Standards were in place to ensure safe annotation of intravenous solutions. These standards consist of three infusion levels and eight principles. The infusion principles are based on common factors that impact the timing and sequence of infusions (►Table 1). Based on these infusion principles, we created three levels of intravenous sequence annotation. The level one standard (based on infusion principles one and two) ensures that necessary safety requirements of intravenous medication administration are used. The level two standard (based on principles three through five) has the potential to reduce adverse drug reactions (ADRs). The level three standard (based on principles six through eight) may improve the effectiveness of drug treatment.

The fundamental component of the PCSA system is the integration of the eight pharmacy infusion knowledge databases. These databases cover all 256 intravenous medications on the hospital formulary. Infusions were analyzed for sequence annotation utilizing package inserts, the "New Edition of Pharmacology (17th edition),"[13] drug manuals, and more than 900 other references. In addition to the dosing frequency, the other seven databases are designed to provide several prompts in the "drug administration reminder" column of the PCSA system, such as "time limit," "incompatible," "pre-medication," "sequence-dependent," "irritant," "chronotherapeutics," and "adjuvant." ►Fig. 1 shows a screen capture of the PCSA system with the highlight of the drug administration reminder column.

After the implementation of the infusion knowledge databases, a computerized annotation module was developed. Both the knowledge databases and the annotation module were embedded into the hospital PIVAS information system to achieve an automatic sequence annotation of intravenous infusions (►Fig. 2).

The correct rate of sequence annotation was assessed by experienced pharmacists to check the quality of the PCSA system. The correct annotation rate was calculated by dividing the number of correct annotations of infusion sequence by the total number of annotation and multiplying by 100. The correct annotation refers to sequences that conform to the Hospital Infusion Standards.

An example of the functioning PCSA system for a patient with a malignant esophageal tumor is given below. The patient is prescribed pantoprazole, ondansetron, leucovorin, 5-fluorouracil, and α-mannan peptide, all to be administered intravenously. Among these drugs, pantoprazole and ondansetron are dosed two times a day, with an interval of more than 8 hours between doses. Throughout a 24-hour period, a total of seven intravenous infusions are administered to this patient. Both pantoprazole and ondansetron are premedications to be infused before chemotherapy drugs (leucovorin and 5-fluorouracil) to prevent

Table 1 Common factors that impact the timing and sequence of intravenous infusions

Factors	Consideration
1.Beyond-use-date (BUD)	Stability. Infuse the medication with the shortest BUD within the same batch (following the specific order of immediate use → use within 1 hour → use within 2 hour, etc.)
2.Infusion incompatibility	Avoid tubing flush. Schedules a third infusion to separate the two incompatible infusions or flushes the IV tubing in-between incompatible infusions when a third infusion cannot be scheduled
3.Premedications before chemotherapy drugs	Avoid side-effects. Infuses anti-nausea medications first to prevent chemotherapy-induced nausea
4.Sequence-dependent chemotherapy drugs	Pharmacokinetics and pharmacodynamics. For example, infuse paclitaxel before cisplatin in the combination therapy to reduce neutropenia[7]
5.Vein-irritant drugs	Vein protection. Infusing the most vein-irritating drug first
6.Chrono-pharmacology	Time of effect. Schedules high-dose glucocorticoid infusion between 7:00 a.m. and 8:00 a.m.[9]
7.Therapeutic drugs before adjuvant drugs	Achieves optimal therapeutic effects
8.Dosing frequency	Standardizes administration times

Abbreviation: IV, intravenous.

批次	序号	用药提示	* 药品名称	药品规格	每次用量	用量单位	频次	每次数量	数量单位
1	No.1	时限/预防(治疗)	0.9%氯化钠注射液(双瓶)	100ml	100	ml	BID	1	袋
			注射用兰索拉唑(上海)	30mg/支	30	mg		1	支
1	No.2	辅药	0.9%氯化钠注射液(双瓶)	250ml	250	ml	BID	1	袋
			▲醒脑静注射液(10ml)	10ml/支	20	ml		2	支
2	No.3	预防(治疗)	0.9%氯化钠注射液(双瓶)	100ml	100	ml	BID	1	袋
			盐酸格拉司琼注射液	3mg:3ml/支	3	mg		1	支
2	No.4		0.9%氯化钠注射液(双瓶)	250ml	250	ml	QD	1	袋
			胞二磷胆碱注射液	2ml:0.1g/支	0.5	g		5	支
4	No.5	时限/预防(治疗)	0.9%氯化钠注射液(双瓶)	100ml	100	ml	BID	1	袋
			注射用兰索拉唑(上海)	30mg/支	30	mg		1	支
4	No.6	辅药	0.9%氯化钠注射液(双瓶)	250ml	250	ml	BID	1	袋
			▲醒脑静注射液(10ml)	10ml/支	20	ml		2	支
4	No.7	预防(治疗)	0.9%氯化钠注射液(双瓶)	100ml	100	ml	BID	1	袋
			盐酸格拉司琼注射液	3mg:3ml/支	3	mg		1	支

Fig. 1 A screen capture of the PCSA system. PCSA, Pharmacy Intravenous Admixture Services Clinical Decision Support Sequence Annotation. The first eight columns from left to right are batch number, sequence number, drug administration reminder, drug name, drug strength, dose, unit, and dosing frequency.

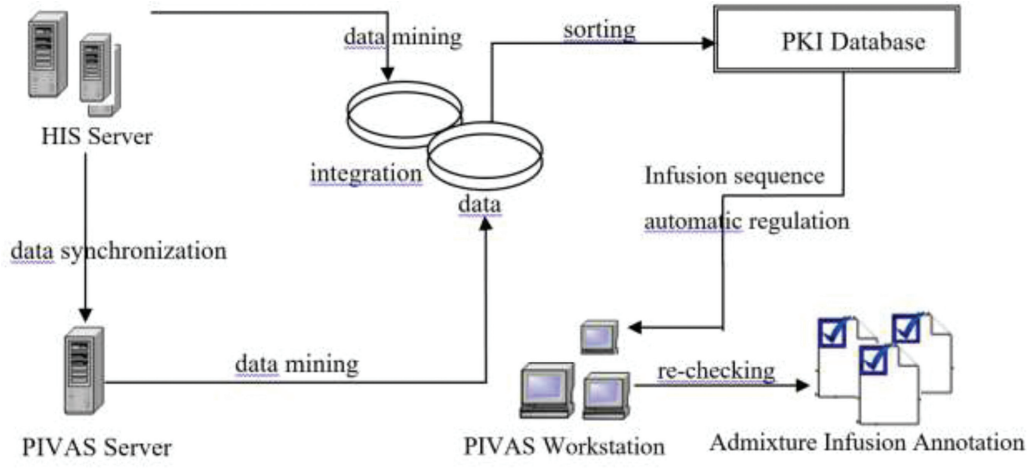

Fig. 2 The PIVAS Clinical Decision Support Annotation System. HIS, hospital information system; PIVAS, Pharmacy Intravenous Admixture Services; PKI, pharmacy knowledge information.

gastric mucosal damage, vomiting, and other adverse reactions. However, pantoprazole has a BUD of 4 hours, and ondansetron should be administered 30 minutes before chemotherapy. For this reason, pantoprazole should be infused/given before ondansetron. Ondansetron and 5-fluorouracil are incompatible when infused sequentially, requiring the medications to be separated by a third infusion or have tubing flushed in-between the two infusions. Leucovorin and 5-fluorouracil are sequence-dependent chemotherapy drugs to promote a synergistic effect, as infusing leucovorin before 5-fluorouracil may increase the efficacy of 5-fluorouracil.[14] The α-mannan peptide is used as an adjuvant treatment to improve the immune function after malignant tumor radiotherapy and chemotherapy. Based on the above information, the PCSA system indicates respective prompts for these intravenous bags in the "drug administration reminder" column of the PCSA system: "pre-medication" (pantoprazole, ondansetron), "time limit" (pantoprazole), "sequence-dependent" (leucovorin and 5-fluorouracil), "incompatible" (ondansetron and 5-fluorouracil), and "adjuvant" (α-mannan peptide). Finally, the PCSA module annotates the seven intravenous infusions as follows: pantoprazole (#1, #6), ondansetron (#2, #7), leucovorin (#3), 5-fluorouracil (#4), and α-mannan peptide (#5). It is worth noting that in certain scenarios, there may be situations where more than one infusion sequence is appropriate according to the Hospital Infusion Standards.

Statistical Analysis

For descriptive analysis, continuous variables are expressed as means and standard deviations, while categorical variables are expressed by frequencies and percentages. Comparisons are made using chi-square analysis for categorical

variables and *t*-test for continuous variables. A *p*-value of < 0.05 is considered statistically significant. All analyses were performed in SPSS Statistics 18.0 (IBM SPSS, United States).

Results

Evaluating the Utility Indicators of the PIVAS Clinical Decision Support Sequence Annotation System

Before providing sequence annotation of intravenous infusions for nurses, a tubing flush (20–50 mL 0.9% normal saline NS or 5% dextrose) was performed with each intravenous infusion medication change to avoid incompatibility per the hospital nursing protocol. ►Table 2 shows that compared with phase 1 manual annotation, there were significant differences in the percentage of hospital wards having intravenous medication infusion sequence annotated in both phase 2 and phase 3 (100% vs. 4.65%, chi-square = 180.95, $p < 0.001$; 100% vs. 4.65%, chi-square = 180.95, $p < 0.001$), percentage of patients with their intravenous medication sequence annotated (64.18% vs. 0.52%, chi-square = 90.46, $p < 0.001$; 65.46% vs. 0.52%, chi-square = 92.23, $p < 0.001$), the percentage of intravenous medication orders with infusion sequence annotated (75.67% vs. 0.77%, chi-square = 118.78, $p < 0.001$; 74.01% vs. 0.77%, chi-square = 113.69, $p < 0.001$), and the number of tubing flushes per ward per day (118.51 vs. 2115, $p < 0.001$; 132.42 vs. 2115, $p < 0.001$). However, there were no significant differences between the mentioned outcomes in phase 3 when compared with phase 2.

Compared with phase 1, there were substantial cost savings in tubing flushes in phase 2 and phase 3 (phase 2 saved 287,964 USD/year, and phase 3 saved 285,918 USD/year). These cost savings were due to the separation of incompatible intravenous solutions through sequence annotation to minimize tubing flushes. However, the tubing flushes cost between phase 3 and phase 2 remained about the same as both phases already had infusion sequences annotated.

Evaluating the work Efficiency Indicators of the PIVAS Clinical Decision Support Sequence Annotation System

In phase 1, it took approximately 1.5 hours for the PIVAS pharmacist to accurately annotate intravenous infusions for two to three patients hospitalized at the respiratory ward and the hematology and oncology ward. Based on this observation, to complete the annotation for all 43 hospital wards, 79.23 hours were needed. As can be seen from ►Table 3, compared with phase 1, there were significant differences in both phase 2 and phase 3 with regards to the pharmacist time spent on annotation (90.6 vs. 4,753.57 minutes, $p < 0.001$; 0.05 vs. 4,753.57 minutes, $p < 0.001$) and the nursing time spent on flushing tubes (1,244.94 vs. 21,684.8 minutes, $p < 0.001$; 1,369.51 vs. 21,684.8 minutes, $p < 0.001$). There was no significant difference in the time nurses spent on flushing tubes between phases 2 and 3 (1,244.94 vs. 1,369.51 minutes, $p = 0.33$). However, significantly less time was required for pharmacist annotation when comparing phase 2 and 3 (90.6 vs. 0.05 minutes, $p < 0.001$).

Evaluating of the Infusion Safety Indicators of the PIVAS Clinical Decision Support Sequence Annotation System

Compared with phase 1, in phase 2 and phase 3 there were significant differences in the number of bags with changes in liquid properties in the infusion tube caused by incompatibility (3 vs. 16, chi-square =12.01, $p = 0.001$; 1 vs. 16, chi-square =18.69, $p < 0.001$), and the number of bags with changes in the properties of the compounded products caused by BUDs (0 vs. 6, chi-square = 7.43, $p = 0.006$; 0 vs. 6, chi-square = 8.18, $p = 0.004$). However, there were no

Table 2 The utility indicators of the PIVAS clinical decision support sequence annotation system

Evaluation index	Phase 1: Manual annotation (January 1 to September 31, 2017)	Phase 2: Computer-aided manual annotation (January 1 to September 31, 2018)	Phase 3: Automated computer annotation (January 1 to September 31, 2019)
Total IV bags compounded (*n*)	248,500	307,700	338,800
Wards with sequence annotated (%)	4.65	100[a] ($\chi^2 = 180.95$, $p < 0.001$)	100[a,b] ($\chi^2 = 180.95$, $p < 0.001$; $\chi^2 = 0.00$, $p = 1.00$)
Annotated patients (%)	0.52	64.18[a] ($\chi^2 = 90.46$, $p < 0.001$)	65.46[a,b] ($\chi^2 = 92.23$, $p < 0.001$; $\chi^2 = 0.02$, $p = 0.88$)
Annotated IV medication orders (%)	0.77	75.67[a] ($\chi^2 = 118.78$, $p < 0.001$)	74.01[a,b] ($\chi^2 = 113.69$, $p < 0.001$; $\chi^2 = 0.11$, $p = 0.74$)
Number of tubing flushes (times/day)	$2{,}115.00 \pm 65.62$	118.51 ± 27.06[a] ($p < 0.001$)	132.42 ± 38.64[a,b] ($p < 0.001$; $p = 0.22$)
Costs for tubing flushing (USD/year)	305,016	17,052	19,098

Abbreviations: IV, intravenous; PIVAS, Pharmacy Intravenous Admixture Service; USD, United States dollar.
[a]Compared with phase 1.
[b]Compared with phase 2.

Table 3 The work efficiency indicators of the PIVAS clinical decision support sequence annotation system

Evaluation index	Phase 1: Manual annotation (January 1 to September 31, 2017)	Phase 2: Computer-aided manual annotation (January 1 to September 31, 2018)	Phase 3: Automated computer annotation (January 1 to September 31, 2019)
Total IV bags compounded (*n*)	248,500	307,700	338,800
The correct annotation rate (%/d)			98.99 ± 1.00
Amount increased of annotation (bag/d)		118.46 ± 12.30	133.61 ± 24.80
Time required to annotate all hospital patients (min/d)	$4{,}753.57 \pm 301.59$	90.60 ± 33.21^{a} ($p < 0.001$)	$0.05 \pm 0.003^{a,b}$ ($p < 0.001$; $p < 0.001$)
Time spent for nursing tubing flushes (min/d)	$21{,}684.80 \pm 1926.32$	1244.94 ± 326.54^{a} ($p < 0.001$)	$1369.51 \pm 428.64^{a,b}$ ($p < 0.001$; $p = 0.33$)

Abbreviations: IV, intravenous; PIVAS, Pharmacy Intravenous Admixture Service.
[a]Compared with phase 1.
[b]Compared with phase 2.

Table 4 The infusion safety indicators of the PIVAS clinical decision support sequence annotation system

Evaluation Index	Phase 1: Manual annotation (January 1 to September 31, 2017)	Phase 2: Computer-aided manual annotation (January 1 to September 31, 2018)	Phase 3: Automated computer annotation (January 1 to September 31, 2019)
Total IV bags compounded (*n*)	248,500	307,700	338,800
Bags with property changes within the infusion tubing (*n*)	16	3^{a} ($\chi^2 = 12.01$, $p = 0.001$)	$1^{a,b}$ ($\chi^2 = 18.69$, $p < 0.001$; $\chi^2 = 1.20$, $p = 0.27$)
Bags with property changes outside the infusion tubing (*n*)	6	0^{a} ($\chi^2 = 7.43$, $p = 0.006$)	$0^{a,b}$ ($\chi^2 = 8.18$, $p = 0.004$; $\chi^2 = 0.00$, $p = 1.00$)

Abbreviations: IV, intravenous; PIVAS, Pharmacy Intravenous Admixture Service.
[a]Compared with phase 1.
[b]Compared with phase 2.

significant differences between these same outcomes in phase 3 compared with phase 2 (►Table 4).

Discussion

In this report, we described the development of a PIVAS CDS Infusion Sequence Annotation system, the first platform in Chinese hospitals. Our hospital was the first in China to explore this method of annotating intravenous infusion sequences. Throughout the process and patient stay, patient medication orders are constantly changing, creating a very demanding annotation workload. The manual annotation process requires substantial professional and clinical knowledge of compounding pharmacists. We progressed to computer-aided manual annotation with the incorporation of infusion sequence databases and knowledge rules into the CDS of the PIVAS system. Although this process improves efficiency, it still requires pharmacists' manual annotation based on computer prompts. This process is still time-consuming and cannot guarantee the consistency of annotation among pharmacists. Therefore, we created the PCSA system, which effectively solves problems in workload and consistency. The PCSA system extends the PIVAS pharmacy service from pharmacist prospective prescription order review/verification to the appropriate nursing infusion administration of compounded intravenous admixtures. Comparing the data collected before and after implementation of the PCSA system demonstrates that the PCSA improves the work efficiencies of pharmacists' annotation and nurses' administration, reduces the cost of infusion tubing flushes, and enhances the safety of intravenous infusions.

As can be seen from ►Table 2, before the implementation of sequence annotation for all intravenous bags, nurses have to flush tubing devices in-between sequential infusions to avoid incompatibilities per hospital policy. Many of these sequential infusions, however, are compatible without the needs of tubing flushes. With the computer-aided manual annotation (phase 2) and the automated PCSA system (phase 3), two incompatible infusions are either separated by a third infusion or a tubing flush is clearly instructed for nursing staff. The practice significantly reduces the numbers and cost of tubing flushes. The cost of tubing flush decreased 94.41% and 93.74% in phase 2 and phase 3, respectively.

The PCSA system significantly improves the work efficiency of PIVAS pharmacists. As can be seen from ►Table 3, it only took approximately 0.05 minute to complete the sequence annotation in phase 3 for all hospital wards. The PCSA system

also had a correct annotation rate of 98.99% The correct annotation refers to sequences that conform to the Hospital Infusion Standards. The annotating efficiency of the PCSA system far exceeded both phase 2 and phase 1. Nurses spent less time performing tubing flushes, a decrease of 94.26% in phase 2 and 93.68% in phase 3. This allows nurses and pharmacists to perform more patient care activities.

The safety of infusions improved in both phase 2 and phase 3 as shown in ►Table 4. The numbers of incompatibilities between consecutive infusions were reduced, and the stability of infusion admixtures improved by infusing bags within the BUDs. Besides the work efficiency improvement, infusion safety improvement, and cost savings, the PCSA system may impact treatment efficacy through sequence scheduling when considering medication chrono-pharmacology and synergistic interactions.

Our research evaluated the impact of the electronic health record (EHR) system on the medication use process. The improved work efficiency and cost savings are significant when comparing phases 2 and 3 with phase 1 (pre-intervention). However, specific parameters are not significantly different when comparing phase 3 and phase 2, as in both phases, EHR technology is utilized. In recent years, medical information systems have been developed to improve medication safety. For example, the utilization of technology reduces prescribing errors in pediatric intensive care and reduces errors in the ordering of total parenteral nutrition in the newborn intensive care unit.[15,16] Another study evaluated the impact of a novel analytic system to detect apparent large overdoses ($\geq$ 500%) and explain the sociotechnical factors that drive the error.[17] Our research and these other studies demonstrate that through design changes in the EHR systems, the medication use process can be improved. Our study has the following limitations: (1) the PCSA system currently does not include temporary medication orders or STAT orders in the sequence annotation. A feature can be added in future system upgrade; (2) the impacts of the PCSA system on the treatment efficacy and patients' outcome are not assessed; (3) we did not quantify the avoidance of ADRs with the introduction of the PCSA system; and (4) this is a single-center study and the results may not be generalizable to other pharmacy practices. Future research should also be directed at evaluating the impacts of the PCSA system on reducing health care costs by enhancing infusion efficacy and safety through sequence annotation.

Conclusion

A CDS annotation system for intravenous infusions is developed based on factors impacting the infusion sequences of intravenous medications. The system can standardize the infusion sequence of multiple intravenous infusions prescribed for a patient. The system significantly improves the work efficiency of pharmacists and nurses, ensures the administration safety of intravenous medications, and frees up valuable health care resources to provide the best care possible for patients.

Clinical Relevance Statement

Multiple factors may impact the sequence of intravenous infusions, such as the pharmacokinetic and pharmacodynamic properties associated with each medication. A computerized clinical decision support annotation system can be developed to annotate infusion sequences effectively. The automated annotation system improves the efficiency of pharmacists and nurses and reduces health care costs associated with infusions.

Multiple Choice Questions

1. Which of the following factors should be considered when arranging the infusion sequence of chemotherapy drugs?
   a. Vein irritation.
   b. Premedications before chemotherapy drugs.
   c. Sequence-dependent chemotherapy.
   d. All of the above.

   Correct Answer: The correct answer is option d. When infusing vein-irritant drugs, the most vein-irritating drug should be infused first to protect the vein. Premedications such as anti-nausea drugs should be infused before chemotherapy drugs to prevent or reduce the toxicities of chemotherapy. When infusing chemotherapy drugs, the pharmacokinetics and pharmacodynamics of the medications should be considered to enhance efficacy or minimize side effects.

2. What is wrong with the following statement?
   a. Phase 3 is fully automated sequence annotation.
   b. The time to complete sequence annotation is 0.05 minute in phase 2.
   c. Compared with phase 1, phase 2 significantly saved nurses' flushing time.
   d. There are significant cost savings for tubing flushes in phases 3 and 2.

   Correct Answer: The correct answer is option b. The time to complete sequence annotation is 0.05 minute in phase 3 not phase 2.

Protection of Human and Animal Subjects

No human or animal subjects were included in this project. Our study was reviewed by our institutional IRB and deemed exempt.

Funding

The project was supported by the Key Research and Development Plan Project of Anhui Science and Technology Department (No.1804h08020276).

Conflict of Interest

None declared.

References

1 Zeng S, Wang D, Yan Y, et al. Single-center analysis of the potential inappropriate use of intravenous medications in hospitalized patients in china. Clin Ther 2019;41(08):1631–1637

2 Wang H, Xie X, Liu Z, et al. Evaluation of the inpatient usage of intravenous infusion in 156 hospitals. J Pharm Pract 2017;35(06): 573–576
3 Sutherland A, Canobbio M, Clarke J, Randall M, Skelland T, Weston E. Incidence and prevalence of intravenous medication errors in the UK: a systematic review. Eur J Hosp Pharm Sci Pract 2020;27 (01):3–8
4 Wu YP, Yan Q, Zhang J. Training instructions for national pharmacy intravenous admixture service operation model & inspections management. Beijing: Scientific and Technology Documentation Press: 2016:33
5 Yang Y, Wang J, Ding H, et al. Analysis on the causes of clinical return of PIVAS finished infusions in our hospital and discussion on intervention strategies. China Pharm 2017;28(34):4894–4896
6 Li R, Ren M, Zeng J, et al. Discoloration of compatibility between cefotaxime sodium and ornidazole sodium chloride injection. Chin J Pharmacov 2013;10(04):247–248
7 Mancini R, Modlin J. Chemotherapy administration sequence: a review of the literature and creation of a sequencing chart. J Hematol Oncol Pharm 2011;1(01):17–25
8 Sauerland C, Engelking C, Wickham R, et al. Vesicant extravasation part I: mechanisms, pathogenesis, and nursing care to reduce risk. Oncol Nur Forum 2006;33:1134–1141
9 Scherholz ML, Schlesinger N, Androulakis IP. Chronopharmacology of glucocorticoids. Adv Drug Deliv Rev 2019;151-152:245–261
10 Zeng S, Wang D, Liu W, et al. Overuse of intravenous infusions in China: focusing on management platform and cultural problems. Int J Clin Pharm 2019;41(05):1133–1137
11 Ogawa H, Amano H, Maki H, et al. An updated and more accurate drip infusion solution monitoring system - biomed 2013. Biomed Sci Instrum 2013;49:74–79
12 Amano H, Ogawa H, Maki H, Tsukamoto S, Yonezawa Y, Caldwell WM. A remote drip infusion monitoring system employing Bluetooth. Annu Int Conf IEEE Eng Med Biol Soc 2012;2012:2029–2032
13 The New Edition of Pharmacology. (17th edition). Accessed April 14, 2020 at: http://www.cpa.org.cn/index.php?do=info&cid=74147
14 Wang C, Wu W, Lv Q. Role of clinical pharmacists participating in rational use of antitumor drugs at PIVAS. Shanghai Med Pharm J. 2017;38(07):65–71
15 Howlett MM, Butler E, Lavelle KM, Cleary BJ, Breatnach CV. The impact of technology on prescribing errors in pediatric intensive care: a before and after study. Appl Clin Inform 2020;11(02): 323–335
16 Kirkendall ES, Kouril M, Minich T, Spooner SA. Analysis of electronic medication orders with large overdoses: opportunities for mitigating dosing errors. Appl Clin Inform 2014;5(01): 25–45
17 Lehmann CU, Conner KG, Cox JM. Preventing provider errors: online total parenteral nutrition calculator. Pediatrics 2004;113 (04):748–753