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Systematic evidence review of rates and burden of harm of intravenous admixture drug preparation errors in healthcare settings

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ABSTRACT

Objective: To examine published evidence on intravenous (IV) admixture preparation errors (IAPEs) in healthcare settings.

Methods: Searches were conducted in three electronic databases (January 2005 to September 2015). Publications reporting rates of IAPE and error types were reviewed and categorized into the following error groups: component errors, dose/calculation errors, aseptic technique errors, and composite errors.

Results: Of the 26 articles that met inclusion criteria, 21 reported on the site of IAPEs: central pharmacies (n=7), nursing wards (n=12), and both settings (n=2). Error types and reported rates varied substantially, including wrong drug (~0% to 4.7%), wrong diluent solution (0% to 49.0%), wrong label (3.2% to 99.0%), wrong dose (0.9% to 32.6%), wrong concentration (0% to 53.0%), wrong diluent volume (0.9% to 49.0%), and inadequate aseptic technique (0 to 69.2%). Only two studies directly compared incidence by preparation site and/or method of preparation, finding error incidence to be lower for doses prepared within central pharmacy than on the nursing ward, and lower for automated preparation versus manual preparation. Although eight studies (32%) reported ≥1 errors with the potential to cause patient harm, no study directly linked IAPE occurrences to specific adverse patient outcomes.

Conclusions: The available data suggest a need to continue to optimize the IV preparation process, focus on improving preparation facilities, design and implement preventive strategies, train staff on optimal admixture protocols, and implement a process of standardization. Future research should focus on the development of consistent error subtype definitions, standardized reporting methodology, and reliable, reproducible methods to track and link risk factors with the burden of harm associated with these errors.

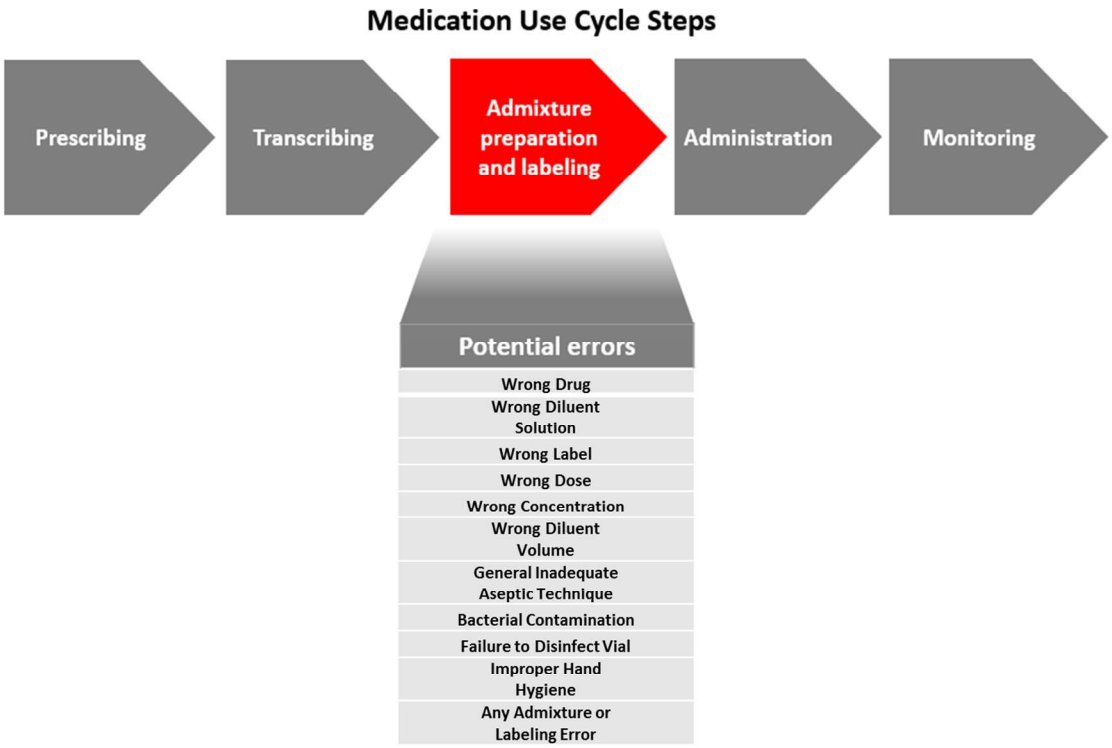
Strengths and limitations of this study

- This is the first systematic review conducted that attempts to categorize intravenous admixture preparation errors (IAPEs) according to both the characteristics of the error and the location and method of IV preparation.
- Although IAPE is a safety concern, its frequency, subtypes, and associated burden of harm are not well understood; thus, the current review presented a thoughtful and valid framework to assess IAPEs within their procedural context.
- This review attempted to include all articles published in English between January 2005 and September 2015 that reported on IAPEs in which healthcare professionals prepared ≥1 dose of IV administered therapy.
- This review is limited by the number of studies identified that reported data on the frequency and/or burden of harm of IAPEs.

INTRODUCTION

Errors in medication preparation and administration can lead to patient harm.[1-3] For example, many preventable adverse events with respect to medication have been linked to errors in dosing (ie, patients receiving higher or lower amounts of medication than intended).[2,4] The medication use cycle for an intravenous (IV) medication involves multiple steps prior to administration, including prescribing and transcription (paper-based orders) in addition to a number of admixture preparation and labeling steps (**Figure 1**).

Figure 1. Intravenous medication use cycle



An IV admixture preparation error (IAPE) can be considered as any deviation from the specifications involved in the admixture preparation and labeling process. An IAPE is a form of medication error—in other words, a preventable adverse event resulting from inappropriate

medication preparation, administration, or use that can lead to patient harm, including death, while the medication is in the control of the healthcare professional, patient, or consumer.[5,6]

IAPEs can be introduced at multiple points during admixture preparation and labeling. These steps can take place on site at a nursing ward or in a central or satellite pharmacy. IV medication doses are typically prepared (1) manually by nurses, either at the bedside or in a ward-based preparation room, (2) manually by pharmacists and pharmacy technicians in a central or satellite clean room under a laminar-airflow hood, or (3) through the use of pharmacy automation technology, which can be partially or fully automated and may be located in clean rooms or clean compartments within the machine. Delivery of the correct dose of an IV admixture to a patient depends on the careful control of many factors, such as the calculation of a patient-specific dose, oversight of procedures utilized for admixture preparation, and labeling practices.[4,7] While research suggests that the highest medication-error rates can be attributed to the prescribing and administration phases of the medication use cycle,[8-10] studies focused on medication preparation practices suggest that there is a significant potential for errors in the IV admixture preparation and labeling phase as well.[8,11-14] It is unknown what proportion of IAPEs go unreported.

In addition to measuring the incidence of IAPEs, it is also important to understand their impact in terms of burden of harm. Two examples of existing frameworks for categorizing patient harm resulting from medication errors are The Institute for Safe Medication Practices (ISMP) high-alert medication lists and The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Medication Error Index. ISMP publishes information and educational resources for healthcare providers on preventing medication errors, and tracks voluntary medication errors reports. Based on these voluntary error reports, ISMP maintains lists

of high-alert medications in outpatient and inpatient settings that have the potential for increased risk of patient harm if used in error.[15] The NCC MERP Medication Error Index groups medication errors into nine possible categories, ranging from non-errors (situations in which errors may occur) to errors resulting in patient death.[16] These categories also include near-miss situations in which an error occurred but did not reach the patient or cause harm. ISMP uses the NCC MERP Medication Error Index in its medication error database.

Much of the prior published research focusing on the prescription or administration of IV therapies has failed to describe or distinguish between errors that arise as a result of the admixture preparation process versus errors associated with incorrect prescribing or administration.[17-20] With this systematic review, our objective is to identify the incidence of IAPEs (overall and by subtype) reported across institutional healthcare settings and to understand the frequency of error subtypes and associated burden of patient harm attributable to IAPEs as reported in the published literature.

METHODS

Identification of literature and data sources

For the purposes of this review, an IAPE was defined as an error or deviation at any step within the admixture preparation process where the drug container was physically handled or manipulated by a healthcare professional. A broad search strategy was developed to identify all studies (published from January 2005 to September 2015) that mention any type of IAPE in an institutional healthcare setting, which included reports relating to wrong drug, wrong diluent solution, wrong label, wrong dose, wrong concentration, wrong diluent volume, and inadequate

aseptic technique. Dose omission errors were considered to be errors related to administration rather than preparation and, thus, were not included as a focus in this study. Near-miss and actual errors (those that did reach patients) were both included. The review was structured based on PICOS (patients, intervention, comparator, outcomes, and study design) criteria (**Table 1**).

Table 1. PICOS Criteria

Patient/Problem	Incorrect preparation of IV admixtures within an institutional healthcare setting (acute or long-term care) by a licensed healthcare professional (nursing and/or pharmacy staff and/or physician) team member
Intervention	Preparation of an IV admixture
Comparison	Automated versus manual preparation methods(studies were not required to demonstrate both) Central pharmacy versus on-unit (on the nursing ward) preparation location (studies were not required to demonstrate both)
Outcome	Incorrectly prepared or labeled IV admixture, which may or may not have reached a patient: • Wrong drug or diluent • Wrong dose, concentration, or volume • Wrong, inaccurate, or omitted label • Contaminated admixture or failure to follow hygiene or sterility protocols • A combination of the above
Study Types	**Inclusion criteria:** Observational studies for which numerator (number of doses impacted or number of errors) and denominator (number of eligible doses or opportunities for error) are discernible **Exclusion criteria:** Studies in which isolated contamination volumes are reported but for which total batch size is unknown fail to qualify for consideration Error report logs for which number of errors is known but associated number of prepared doses is not also fail to qualify

PICOS, patients, intervention, comparator, outcomes, and study design (criteria); IV, intravenous.

Systematic review process

Three electronic databases were searched for relevant literature reporting on IAPE: Ovid MEDLINE, EMBASE, and International Pharmaceutical Abstracts. The initial search was conducted on February 6, 2014, with supplementation on September 4, 2015 to include articles published during the interim. Aggregate results include articles published in English between January 2005 and September 2015 that involved studies in human subjects in which a healthcare professional prepared ≥1 doses of IV administered therapy (medication or total parenteral nutrition). Key search terms and limits used in the systematic review are shown in **online supplementary Table S1**. Screenings for relevant literature citations that appeared in the publications were made during the review process to identify any pertinent, additional publications up to September 2015. To be included in this systematic review, references had to meet the inclusion/exclusion criteria detailed in the next section. Duplicate articles were removed electronically prior to manual review. Titles of the papers and abstracts captured in the electronic search results were screened by two reviewers for relevancy according to prespecified criteria. If the titles did not provide sufficient information for screening, the abstract or full-text articles were then reviewed to discern whether the publication met inclusion criteria. All publications that met entry criteria for the review were obtained as full-text articles and then reassessed by the reviewers against the review criteria. The review process was fully compliant with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21]

Inclusion and exclusion criteria

Publications reporting on a randomized, controlled trial, prospective cohort study, observational quality audit, descriptive study, quasi-experimental study, or quality-improvement study were selected for inclusion. Quasi-experimental studies, quality-improvement studies, and descriptive

studies were eligible if they included sufficient data on the number of doses prepared. While systematic reviews reporting on these study types were not included, their respective reference lists were reviewed to identify potentially relevant studies. Publications were not limited to a single geographic or physical study location and may have occurred in the hospital or any other institutional or outpatient healthcare setting.

Publications and studies were included for review if they either reported incidence of IAPE or provided sufficient detail for incidence calculation. These errors included incorrectly dispensed medication as well as near-misses that were caught by the study observer prior to administration. Errors also had to originate from a healthcare professional (eg, nurse or pharmacist). Studies reporting patient or informal caregiver medication errors were not included. To be included, studies were required to report original data on IAPEs, including a denominator to allow for incidence calculations.

Articles and studies that only described errors in prescribing, transcription, administration, and monitoring were not included. In addition to all articles that failed to meet the aforementioned inclusion criteria, the following article types were also excluded: conference abstracts, case reports, simulations, and survey findings.

Data extraction

The data extracted from relevant articles for analysis included year of publication, country of origin, study period, patient population, definition of error, IV preparation location (eg, central or satellite pharmacy or nursing ward), care setting (eg, critical care, general nursing ward), type of therapy, method of error detection, and error incidence. Data were extracted and scored independently by two separate reviewers, with introduction of a third reviewer in the case of

scoring discrepancies, with all differences being resolved by consensus. Each review team included ≥one pharmacist, given their professional knowledge and understanding of drug preparation. The methodological rigor of each study was critically appraised and scored using the Hawker method.[22] This method employs nine criteria to evaluate for each study: 1) abstract and title, 2) introduction and aims, 3) method and data, 4) sampling, 5) data analysis, 6) ethics and bias, 7) results, 8) transferability or generalizability, and 9) implications and usefulness. For each criterion, studies were scored as: good (score 4), fair (score 3), poor (score 2), or very poor (score 1). A mean score was then calculated for each study across all nine criteria, and the overall quality of each study was likewise scored from good to very poor.

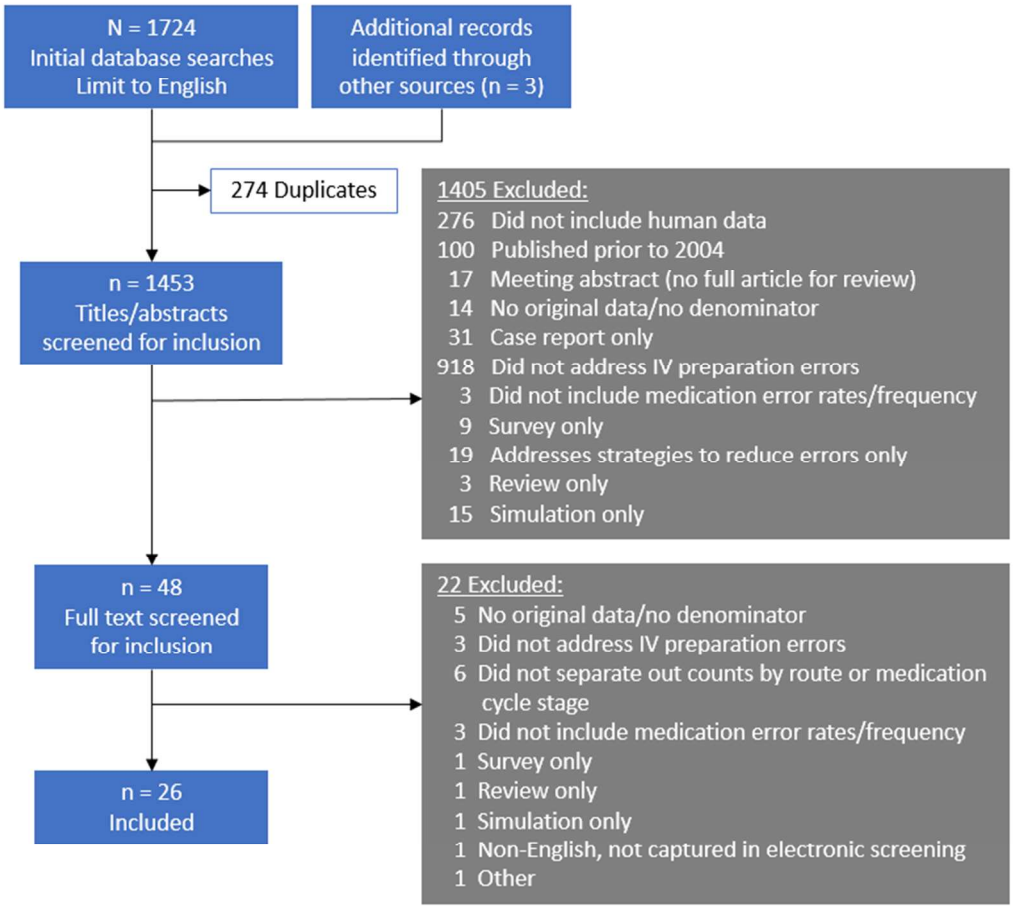
For the purposes of this review, IAPEs were grouped into one of four categories based on the characteristics of the error and the location and method of IV preparation. Component errors were defined as all those that result from selecting an incorrect ingredient (ie, wrong drug or wrong diluent solution), or applying an incorrect, incomplete, or inaccurate label (ie, wrong label) to the admixture. Dose/calculation errors were defined as those involving the use of an incorrect calculation to determine dose and/or diluent amount, or use of a diluent volume not in accordance with the package insert (ie, wrong dose, wrong concentration, and wrong diluent volume). Aseptic technique errors involved a breakdown in the process designed to minimize the potential for antimicrobial contamination (ie, inadequate aseptic technique, bacterial contamination, failure to disinfect vial, and improper hand hygiene). The category of composite errors was used to describe IAPEs reported in aggregate, without differentiating between IAPE subtypes.

This study was registered with the PROSPERO international database of systematic reviews (CRD42014010418) to comply with PRISMA guidelines.

RESULTS

Electronic database searches yielded 1724 English language publications for review. Additional sources (hand searches of publication reference lists) identified another three publications for evaluation. After removing duplicates and screening for inclusion and exclusion criteria, 26 articles were included in the final analysis (**Figure 2**).[3,23-47] Of the 26 articles, 5 (19%) were rated good quality,[27,32,36,43,44] 17 (65%) were fair quality,[3,23-26,28-31,34,35,37-39,41,42,46] and 3 (12%) were poor quality[33,40] after assessment using the Hawker method. The quality of one study (4%) could not be fully scored due to a missing data table in the available publication.[45]

Figure 2. PRISMA study inclusion flow diagram



Study characteristics

A summary of the study characteristics, patient populations, and types of IV therapies described in the 26 publications is illustrated in **Table 2**. Collectively, the publications reported international data, with 9 of the 26 studies (35%) conducted in Europe (Germany: 3[24,28,44]; France: 1,[25] Greece: 1,[40] Italy: 1,[34] Spain: 1,[37] United Kingdom [UK]: 1,[41] France, Germany, and the UK: 1 multinational study).[26] Five studies (19%) were conducted in the United States.[27,33,38,39,42] There were four studies (15%) from Iran,[29,30,45,47] two from Brazil (8%),[23,31] and one each (4%) from Australia,[3] Canada,[36] Malaysia,[35] Vietnam,[43] China[46] and Mexico.[32]

The majority of references (22 [85%]) reported single-center studies (**Table 2**). One study (4%) reported data from two major teaching hospitals[3], and three studies (12%) were conducted at three hospitals.[23,26,47]

Table 2. Study Characteristics

Study	Geographical Location(s)	Centers, n	Patient Population	Study Design	Observational Technique	Type of Intravenous Admixture	Location of Intravenous Admixture Preparation	Method of Intravenous Admixture Preparation	Patient Impact Measured (Yes / No)
Anselmi et al. 2007[23]	Brazil	3	General inpatient units	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	No
Bertsche et al. 2008[24]	Germany	1	General inpatient units and ICU	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes
Castagne et al. 2011[25]	France	1	Oncology inpatients	Single arm	Final concentration of admixture	Chemotherapy	Central pharmacy	Automated	No
Cousins et al. 2005[26]	France Germany UK	3	General medical and surgical inpatients	Single arm	Direct observation (participants in France and Germany were blinded to study purpose)	Multiple IV therapies	Nursing ward	Manual	No
Crill et al. 2010[27]	US	1	Critical care (NICU)	Single arm	Bacterial culture	Intravenous fat emulsion	Central pharmacy	Manual	Yes
Dehmel et al. 2011[28]	Germany	1	Critical care (ICU)	Comparative	Final concentration of admixture	Multiple IV therapies	Central pharmacy vs nursing ward	Automated vs manual	No
Ding et al. 2015[46]	China	1	General surgery inpatients	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes

Fahimi et al. 2007[29]	Iran	1	Critical care (ICU)	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes
Fahimi et al. 2008[30]	Iran	1	Critical care (ICU)	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes
Hoefel et al. 2006[31]	Brazil	1	General units and ICU	Single arm	Direct observation	Antibiotic (cefepime)	Nursing ward	Manual	No
Khalili et al. 2013[47]	Iran	3	Adult and pediatric inpatients	Comparative	Bacterial culture	Multiple IV therapies	Central pharmacy vs nursing ward	Manual	No
Macias et al. 2005[32]	Mexico	1	Critical care (NICU)	Single arm	Bacterial culture	Multiple IV therapies	Nursing ward	Manual	No
MacKay et al. 2009[33]	US	1	Pediatric trauma unit	Interventional	Cross-check	Multiple IV therapies	Central pharmacy	Automated	No
Masini et al. 2014[34]	Italy	1	Inpatient and outpatient oncology	Comparative	Final concentration of admixture	Chemotherapy	Central pharmacy	Automated vs manual	No
Moniz et al. 2014[42]	US	1	Pediatric inpatients	Single arm	Direct observation; Pharmacists reviewed digital photos of each preparation step via a web application	Multiple IV therapies	Central pharmacy	Automated	Yes
Nguyen et al. 2014[43]	Vietnam	1	Critical care (ICU / PSU)	Interventional	Direct observation (participants were blinded to study purpose)	Multiple IV therapies	Not specified	Manual	Yes
Niemann et al. 2014[44]	Germany	1	Pediatric inpatients	Interventional	Direct observation	Multiple IV therapies	Not specified	Manual	Yes

Ong et al. 2013[35]	Malaysia	1	General and acute care, adult and pediatric inpatients	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	No
Parshuram et al. 2006[36]	Canada	1	Pediatric oncology (not specified if inpatient or outpatient)	Single arm	Final concentration of admixture	Chemotherapy	Not specified	Not specified	No
Rodriguez-Gonzalez et al. 2011[37]	Spain	1	Gastroenterology inpatients	Single arm	Direct observation (participants were blinded to study purpose)	Multiple IV therapies	Not specified	Not specified	Yes
Sacks et al. 2009[38]	US	1	General adult and pediatric inpatient units and ICU	Single arm	Incident reports	Total parenteral nutrition	Central pharmacy	Automated	Yes
Seger et al. 2012[39]	US	1	Oncology inpatients	Comparative	Direct observation	Chemotherapy	Central pharmacy	Automated vs manual	Yes
Skouroliakou et al. 2005[40]	Greece	1	Neonatal inpatients	Comparative	Cross-check and direct observation	Total parenteral nutrition	Not specified	Automated vs manual	No
Tavakoli-Ardakani et al. 2013[45]	Iran	1	Hematology and oncology inpatients and outpatients	Single arm	Direct observation	Chemotherapy	Nursing ward	Manual	No
Westbrook et al. 2011[3]	Australia	2	General and surgical inpatients	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes

Wheeler et al. 2008[41]	UK	1	Critical care (neurological) inpatients	Interventional	Cross-check	Multiple IV therapies	Nursing ward	Manual	No

Method of preparation was assumed to be manual for studies in which IV admixture preparation occurred in the nursing ward, and no other information regarding method of preparation was provided.

ICU, intensive care unit; IV, intravenous; NICU, neonatal intensive care unit; PSU, post-surgical unit; UK, United Kingdom; US, United States.

Various methods of detection were used including direct observation in 15 studies (58%),[3,23,24,26,29-31,35,39,42-46], analysis of final concentration in four studies (19%),[25,28,34,36,41] bacterial culture in three studies (12%),[27,32,47], cross-checking in three studies (8%)[33,40,37], and incident reports in one study (4%).[38] In several studies using the direct observation method, nurses or pharmacists preparing the IV admixtures consented to participate but were not fully aware of the study aims to avoid influencing their behavior.[17,37,43] Four studies (15%) reported on the accuracy of IV preparation before and after an intervention,[33,41,43,44] five studies (19%) compared IV admixture preparation locations or methods,[28,34,39,40,47] and the remaining 17 publications (65%) were single-arm studies.[3,23-27,29-32,35-38,42,45,46]

Seven publications (27%) reported on IV therapies prepared for use in pediatric populations only,[27,32,33,36,40,42,44] three studies (12%) included a mix of pediatric and adult patients,[35,38,47] six studies (23%) described treatment of adult patient populations,[3,28,31,37,39,41] and the remaining 10 publications (38%) did not characterize the age groups studied.[23-26,29,30,34,43,45,46] Seven studies (27%) were exclusively in critical care settings,[27-30,32,41,43] and the remaining 19 publications (73%) reported on treatment given either on general wards, both intensive care units and general wards, or were not specified.[3,23-26,31,33-40,42,44-47]

A total of 21 studies reported the IV preparation site. Of those studies, 12 publications (57%) reported preparation on the nursing ward[3,23,26,29-32,35,41,45,46] and 7 (33%) reported use of central pharmacies.[24,25,27,33,34,38,39,42] Two studies (10%) compared rates of IAPEs in the nursing ward and a central pharmacy.[28,47]

Of the 26 publications, 17 (65%) included >1 type of IV therapy.[3,23,24,26,28-30,33,35,37,41-44,46,47] Five studies (19%) evaluated only chemotherapy,[25,34,36,39,45] three studies (12%) reported

only parenteral nutrition or IV lipid emulsions,[27,32,38,40] and one study (4%) only evaluated antibiotic (cefepime) preparation errors.[31]

While IAPEs were not consistently linked to individual patient outcomes in the studies surveyed, nearly half of the studies attempted to assess the potential for patient impact in some way. Twelve (46%) of the publications included in this review reported on the severity of harm or potential for harm arising from identified IAPEs (see **online supplementary Table S2**), [3,24,27,29,30,37-39,42-44,46] eight (67%) of which reported ≥1 errors to result in various degrees of harm,[3,24,38,39,42-44,46] and four (33%) having reported no errors to have resulted in adverse outcomes or to have presented a major patient risk.[27,29,30,37]

Of the 12 studies that reported on burden of harm, three (25%) used the NCC MERP medication error index[48] to score identified errors;[29,37,38] while six studies (50%) relied on clinician assessment or expert panel for determination of error severity.[3,24,39,42-44] Among the six studies which used clinician assessment or expert panel, two of the study teams (Niemann et al.[44] and Nguyen et al.[43]) assessed errors based on clinical relevance rather than assigning a score based on patient harm or potential for harm. The remaining three studies each took a different approach to estimating patient harm.[27,30,46] Ding and colleagues[46] were the only authors to record whether the error was associated with a drug found on the ISMP list of high-alert medications. Crill and colleagues[27] did not have a system for rating error severity, but did note that no contamination errors resulted in patient infections. Lastly, the 2008 study by Fahimi and colleagues[30] did not describe a specific system for rating error severity, but noted that none of the errors identified resulted in adverse events or major risks to patients.

Categorization and incidence of IAPEs

Errors identified in the selected studies were grouped into four broad categories: component errors, dose/calculation errors, aseptic technique errors, and composite errors, as detailed in the Methods section. Errors of the same subtype were frequently defined slightly differently among studies; full descriptions of the error subtype definitions are shown in **online supplementary Table S3**. Incidence values for error subtypes are presented in **Table 3**.

Table 3. Summary of Reported IAPE Incidence by Error Subtype

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
Anselmi et al. 2007[23]	Numerator: errors (including near-misses) Denominator: Doses prepared	Site 1: 0/804 Site 2: 0/100 Site 3: 1/487			Site 1: 8/804 Site 2: 2/100 Site 3: 36/487							Across all sites: 118/1391
	Incidence:	**0.00%–0.20%**			**0.90%–7.40%**							**8.48%**
Bertsche et al. 2008[24]	Numerator: events Denominator: drug-handling processes							218/315				
	Incidence:							**69.20%**				
Castagne et al. 2011[25]	Numerator: errors (102 near-misses; 544					646/7382						

	errors)								
	Denominator: doses prepared								
	Incidence:				**8.80%**				
Cousins et al. 2005[26]	Numerator: errors (not including near-misses) Denominator: doses prepared	UK: 0/273 GER: 0/425 FR: 0/100	UK: 2/273 GER: 208/425 FR: 18/100	UK: 118/273 GER: 421/425 FR: 20/100	UK: 1/273 GER: 7/425 FR: 5/100		13 /798 total		UK: 295/299 GER: 245/425 FR: 4/100 UK: 299/299 GER: 403/425 FR: 9/100
	Incidence:	**0.00%–0.00%**	**1.00%–49.00%**	**20.00%–99.00%**	**1.00%–5.00%**		**2.00%**		**4.00%–99.00%** **9.00%–100.00%**
Crill et al. 2010[27]*	Numerator: positive bacterial cultures Denominator: syringes prepared						3/90	3/90	
	Incidence:						**3.30%**	**3.30%**	
Dehmel et al. 2011[28]†	Numerator: errors Denominator: doses prepared				±5% deviation: 16/100 ±10% Deviation: 5/100				
	Incidence:				**5.00%–16.00%**				
Dehmel et al. 2011[28]‡	Numerator: errors				±5% deviation: 53/100				

	Denominator: doses prepared				±10% deviation: 22/100	
	Incidence:				**22.00%–53.00%**	
Ding et al. 2015[46]§	Numerator: errors Denominator: TOE (ordered and unordered doses)			50/593		54/593
	Incidence:			**8.43%**		**9.10%**
Fahimi et al. 2007[29]	Numerator: errors (including near-misses) Denominator: doses administered	2/43	4/43	14/43		
	Incidence:	**4.65%**	**9.30%**	**32.60%**		
Fahimi et al. 2008[30]¶	Numerator: errors (including near-misses) Denominator: doses prepared	49/524		38/524		
	Incidence:	**9.35%**		**7.25%**		
Hoefel et al.	Numerator:			14/99	6/99	

2006[31]	errors				
	Denominator:				
	doses				
	administered				
	Incidence:	**14.10%**	**6.10%**		
	Numerator:				
	positive bacterial			Nursing ward:	
				1/92	
Khalili et al.	cultures				
				Central	
2013[47]	Denominator:				
				pharmacy: 0/17	
	doses prepared				
	Incidence:			**0.00–1.10%**	
	Numerator:				
	positive bacterial				
Macias et al.	cultures			1/51	
2005[32]‖	Denominator:				
	doses prepared				
	Incidence:			**1.45%**	
	Numerator:				
	errors				
MacKay et al.	Denominator:				0.66/1000
2009[33]**	1000 doses				
	prepared				
	Incidence:				**0.07%**
Masini et al.	Numerator:		5% relative		
2014[34]††	errors		error: 1/333		

	Denominator: doses prepared				10% relative error: 4/333				
	Incidence:				**0.30%–1.20%**				
Moniz et al. 2014[42]‡‡	Numerator: errors	8/	3/	857/		11/			2883/
	Denominator: doses prepared	425,683	425,683	425,683		425,683			425,683
	Incidence:	**~0.00%**	**0.00%**	**0.20%**		**~0.00%**			**0.68%**
Nguyen et al. 2014[43]§§	Numerator: errors (including near-misses) Denominator: TOE (administered and omitted doses)	ICU: 1/236 PSU: 1/280		ICU: 27/236 PSU: 17/280					ICU: 159/236 PSU: 204/280
	Incidence:	**0.36%–0.42%**		**6.10%–11.40%**					**67.3%–72.90%**
Niemann et al. 2014[44]	Numerator: errors Denominator: drug-handling processes		38/233			115/233			138/233
	Incidence:		**16.00%**			**49.00%**			**59.00%**
Ong et al. 2013[35]	Numerator: errors (including	1/349	1/349	11/349		61/349		307/349	81/349

	near-misses) Denominator: doses administered							
	Incidence:	**0.28%**	**0.28%**	**3.20%**	**17.50%**	**88.00%**	**23.20%**	
Parshuram et al. 2006[36]	Numerator: errors Denominator: infusion bags prepared				24/78			
	Incidence:				**31.00%**			
Rodriguez-Gonzalez et al. 2011[37]¶¶	Numerator: errors (including near-misses) Denominator: TOE (observed administrations plus omitted doses)		8/402		32/402			
	Incidence:		**1.99%**		**7.96%**			
Sacks et al. 2009[38]	Numerator: errors Denominator: doses prescribed							18/4730

	Incidence						**0.38%**
Seger et al. 2012[39]‖‖	Numerator: errors Denominator: doses prepared	3/1421			23/184		
	Incidence:	**0.21%**			**12.50%**		
Skouroliakou et al. 2005[40]	Numerator: errors Denominator: solutions prepared				20/941	8/941	
	Incidence:				**2.13%**	**0.85%**	
Tavakoli-Ardakani et al. 2013[45]***	Numerator: errors Denominator: TOE						2705/8322
	Incidence:						**32.50%**
Westbrook et al. 2011[3]	Numerator: errors (including near-misses) Denominator: doses administered	1/568	21/568			121/ 568	
	Incidence:	**0.18%**	**3.70%**			**21.30%**	
Wheeler et al. 2008[41]	Numerator: errors			88/149			

Denominator:	
syringes prepared	
Incidence:	**59.10%**

* Crill et al. 2010[27]. Authors speculate that contamination arose during preparation, but note that it may also have occurred during or after administration.

† Dehmel et al. 2011[28]. Results presented for automated preparation in the centralized pharmacy.

‡ Dehmel et al. 2011[28]. Results presented for manual preparation in the nursing ward.

§ Ding et al. 2015[46]. Wrong dose error rate combines wrong dose, omission, and extra dose.

¶ Fahimi et al. 2008[30]. Wrong dose and wrong diluent volume were combined into one value in the original article.

‖ Macias et al. 2005[32]. This study was designed to observe a sepsis outbreak. Only baseline (pre-outbreak) data are presented in this table.

** MacKay et al. 2009[33]. This study tested automation as an intervention. Only baseline data is presented in this table.

†† Masini et al. 2014[34]. Results presented for manual preparation only.

‡‡Moniz et al. 2014[42]. Wrong volume of drug/diluent (detectable by previous practices), wrong drug volume (not detectable by previous practices), and wrong diluent volume (not detectable by previous practices) are combined in this table as wrong dose.

§§ Nguyen et al. 2014[43]. This was an interventional study. Only baseline data is presented in this table.

¶¶ Rodriguez-Gonzalez et al. 2011[37]. Errors were defined as "wrong reconstitution (volume, fluid)", which is reported in this table as wrong diluent solution, and "wrong dilution (volume, fluid)", which is reported in this table as wrong diluent volume.

‖‖ Seger et al. 2012[39]. Results presented for manual preparation only. Wrong dose and wrong diluent were reported as a combined value in the original article.

*** Tavakoli-Ardakani et al. 2013[45]. This study reported that additional data was collected by error subcategory; however, these data are not present in the available publication.

Unless otherwise noted, all data reported from interventional studies are from the baseline period only.

FR, France; GER, Germany; ICU, intensive care unit; PSU, post-surgical unit; TOE, total opportunities for error; UK, United Kingdom

The error subtype of wrong drug selection was infrequent, with the highest reported rate of 4.7% of total doses.[3,26,29,35] Selection of a wrong diluent solution was reported to have occurred in 7 of 26 publications (27%), with results varying across studies (~0% to 49.0%).[3,26,30,35,37,42,44] Of note, the multicenter, multinational study by Cousins et al.[26] reported that 1.0% to 49.0% of doses administered had been prepared with an incorrect diluent across all study sites. This range is wider than that of the other included studies (0% to 16.0%).[26] Labeling errors were reported in four publications (15%), with reported incidence varying substantially, ranging from 3.2% to 99.0% (20.0 to 99.0% within the Cousins et al. study[27] alone).[26,29,35,41]

Eight publications (31%) captured incidence of wrong dose, and while most of these studies reported incidence below 10%,[23,26,30,42,46] one study did report an incidence over 32%.[29] Wrong drug concentration errors were reported in six publications (23%), with error incidence per total number of IV doses prepared ranging from 0.3% to 53.0%.[25,28,34,36,39,40] While some studies defined a concentration error based on a threshold 5% deviation between the prepared dose and the ideal dose,[28,34,39] the Castagne study used a higher threshold of 20%. [25]

Seven studies (27%) reported errors pertaining to wrong diluent volume,[3,17,31,35,37,40,44] with most studies (four) explicitly defining this error subgroup as any deviation from manufacturer or accepted institutional guidelines for IV preparation.[3,35,37,44] The highest reported error rate (49.0%) was identified by Niemann and colleagues,[44] while the lowest reported incidence (0.9%) was from the Skouroliakou et al. study,[36] although this study reported errors pertaining to overall IV solution volume as opposed to diluent volume alone.

Reported challenges with aseptic technique included general aseptic technique deviations, bacterial contamination, failure to disinfect the vial, and improper hand hygiene. In studies that reported general inadequate aseptic technique deviations, two studies reported incidence below 5% (range: 0% to 3.3%)[24,27,42]; however, the study by Bertsche and colleagues[24] reported an incidence of just under 70%. The variation in incidence presented may be the result of differences in error definitions, as Bertsche and colleagues assessed aseptic technique deviations as any procedural deviation from local hygiene guidelines.[24] The other studies defined aseptic technique errors either based on bacterial cultures[27,32] or report of syringes left uncapped during the preparation process.[42]

Bacterial contamination errors were reported in three studies, with all reporting incidence under 5% (**Table 3**).[27,32,47] Two additional studies report error incidence for both failure to disinfect the vial and improper hand hygiene.[26,35] In particular, the study by Cousins and colleagues[26] presents a wide range of incidence across aseptic technique subtypes (**Table 3**). The Cousins et al. study[26] presented data from three separate institutions located in France, Germany, and the UK, with incidence of aseptic technique errors from the French institution found to be dramatically lower (4.0% for vial disinfection and 9.0% for hand washing). Of note, the authors attribute this difference to the French institution having undergone a recent update to their aseptic preparation methods protocol due to a prior outbreak of Legionnaire's disease within the facility.[26]

Eight (31%) studies reported an overall incidence of IAPEs that combined multiple error subtypes.[23,33,38,42-46] These studies have diverse error definitions and error detection methods; thus, the error incidence ranges widely (0.07% to 72.9%).

DISCUSSION

This systematic review found that IAPEs are ubiquitous across countries and hospital locations, and that the types of errors observed and reported are diverse. Reported error incidence was found to vary widely not only between settings (central pharmacies or nursing wards) but also within these settings across studies. Variability in error detection methods and definitions applied may contribute to the variation in error rates reported across studies.

This review identified studies conducted in Europe, North and South America, and Asia. While different regions, countries, and even individual institutions are likely to have somewhat different standards and practices for IV admixture preparation, differences in methods and terms applied for data collection did not seem to vary any greater between countries than within a single country. In theory, variation among institutions within the same country has the potential to be larger than variation among countries, as local practices may be more flexible than nationally adopted standards. This highlights an important need for international consensus on defining and identifying IAPEs to fully understand the global patient burden.

There was some evidence for the effect of location and method of IV admixture preparation on the incidence of errors. In particular, error rates appear to be lower when IV preparation takes place in central pharmacy settings compared with nursing wards, and lower with automated versus manual preparation. Among studies meeting the inclusion criteria for this systematic review, only Dehmel and colleagues[28] and Khalili et al[47] directly compared error rates identified from a central pharmacy to those from a nursing ward using consistent IAPE definitions across settings. The Dehmel et al. study reported a markedly higher rate of wrong concentration errors using manual preparation in a nursing ward when compared with automated preparation in a central pharmacy (53% vs 16%, respectively).[28] Khalili and colleagues reported

a low rate of bacterial contamination (1.1%) in admixtures prepared on nursing wards, with no instances of contamination in admixtures prepared in central pharmacies, despite use of manual preparation techniques in each setting.[47] Caution should be taken in generalizing this finding, given the limited sample size of 17 preparations in the central pharmacy and 97 on the nursing ward.[47] Thus, while it appears that central pharmacies and automated technologies may reduce IAPEs, further empirical studies are required to substantiate this hypothesis.

In the present systematic review of IAPEs, a patchwork of data emerged from the relevant available literature, in part because no single study design or observational technique is ideal for capturing all the aspects of IV admixture preparation that could result in an error. The majority of studies relied on direct observation of the IV admixture preparation process by a trained observer, while other studies used bacterial culture, measurement of the final admixture concentration, incident reports, and cross-checking against a checklist, computed calculation, or other benchmarks. However, certain error subtypes naturally leant themselves to a specific observational technique, such as bacterial culture for assessing bacterial contamination, laboratory testing for concentration errors, and direct observation for aseptic technique deviations.

The framework used for categorizing IAPEs in this review was developed to facilitate the aggregation of data collected across studies. While inconsistency across reported error definitions precluded additional quantitative aggregation, we hope the classification system used herein is informative to researchers designing future studies, and may help to facilitate more effective standardization of error reporting going forward.

Within IAPE subtypes, the method of error calculation varied in some cases, which impacted the ability to generalize results across studies. The majority of studies reported the

incidence as errors per doses prescribed, prepared, or administered. However, four (15%) studies reported errors per total opportunities for error [37,43,45,46] and two (8%) studies reported errors per total drug-handling processes.[24,44] While using total opportunities for error or drug-handling processes may be insightful for those wishing to understand and optimize the IV medication use cycle from the user perspective, errors per dose may be a more useful measurement for researchers interested in patient impact and outcomes.

Error definitions were also variable within some error subtypes. For instance, thresholds for determining concentration errors ranged from ±5% variance from the label specification to as high as ±20% variance.[25,28,34,36,39,40] Studies reporting IAPE incidence based on a composite of IAPE subtypes were often composed of common elements (eg, wrong drug, wrong concentration), but were sufficiently different that they could not be directly compared. This finding exposes a need for a standardized taxonomy of error subtypes that can be used across a variety of research settings and countries to facilitate meaningful comparisons.

Other factors that may impact error incidence are circumstances, such as either a recent training or sentinel event as described by Cousins et al.,[26] when commenting on proportionally lower aseptic technique deviations observed in the French study site. It was suggested that this finding may be attributed to recent staff training and updated guidelines in the French institution included in the study, prompted by a recent outbreak of Legionnaire's disease at that site. This highlights the impact of staff training not only as a source of potential regional or institutional error variation, but also as a means of reducing error rates. Given the short duration of time between staff training and study implementation, the long-term sustainability of error reduction potentially gained by staff training in the Cousins et al. study was unclear.

In addition to heterogeneous error incidence results, the articles captured in this systematic review used a variety of approaches to measuring the potential burden of patient harm. Several studies used the existing NCC MERP error index[48] to rate and score errors, and the majority of other studies relied upon either local clinician opinion or expert panel. As a result, there is a high degree of variability in terms of how the errors are scored and how potential for patient risk is attributed.

Of the 26 studies included in this review, 12 (46%) provided estimates or general assessments for potentially attributable patient harm or clinical relevance for IAPEs,[3,24,27,29,30,37-39,42-44,46]. Effective and standardized traceability measures are required to link a defect in the admixture process that occurs early within the medication use cycle with later negative patient outcomes. Given the separation in time and physical location between admixture preparation and potential patient physical adverse response, it can be challenging to link potential negative patient outcomes to the admixture/compounding process where unrecognized potential errors may exist.[11] There is a need for robust study designs that allow for the assessment of the association between specific errors incidences and patient outcomes.

Several limitations were present in this systematic review. Our search strategy targeted the broad medical literature, but inclusion of additional databases, such as the Cumulative Index of Nursing and Allied Health Literature may have added nursing specialist publications relevant to this topic. While the quality of publications was generally fair, only five studies (19%) were deemed to be of good quality in terms of methodology and reporting.[27,32,36,43,44] Further, the Hawker method of quality ascertainment is generic, and may not be best suited to capturing the unique challenges of this research topic. Drawing comparisons between the studies remains difficult due to substantial variations in error definitions. As a result, meta-analysis of the current

IAPE literature was not considered appropriate. Lastly, in the majority of studies, documentation of error severity and associated burden of harm was not sufficient to allow for a thorough evaluation of the impact on patient care or the consequences for healthcare facilities.

CONCLUSIONS

This systematic review is the first to categorize IAPEs according to the characteristics of the error and the location and method of IV preparation. It is our hope that future studies may use these categorizations to provide a meaningful framework to assess IAPEs within their procedural context. With improved standardization of IAPE definitions, grouping error subtypes as we have done may facilitate an improved understanding of where errors happen within the IV preparation process and devising solutions to help eradicate them. There is a clear potential burden of harm for patients resulting from IAPEs, and thus a need to continue to optimize the IV preparation process, focusing on improving preparation facilities, designing and implementing preventive strategies, staff training, and implementing process standardization where possible. Future research should focus on the development of consistent error subtype definitions and a standardized reporting methodology as well as reliable and reproducible methods to track and link risk factors and the burden of harm associated with these errors.

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Data Sharing Statement

As the research presented is a systematic literature review of published data, no additional unpublished data are available.

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Contributors

NH: Concept/design, data analysis/interpretation, critical revision of article, approval of article.

IB: Data interpretation, critical revision of article, approval of article.

T H-T: Concept/Design, data interpretation, critical revision of article, approval of article.

PT: Concept/design, data interpretation, critical revision of article, approval of article.

Competing Interests

NH is a former employee and stockholder of Baxter Healthcare Corporation.

IB is an employee and stockholder of Baxter Healthcare Corporation.

T H-T has no relevant competing interests to disclose.

PT is currently under contract to perform other work for Baxter Healthcare Corporation that is unrelated to the current manuscript.

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FIGURE TITLES AND LEGENDS

Figure 1. Intravenous Medication Use Cycle

Figure 2. PRISMA study inclusion flow diagram

IV, intravenous; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

ONLINE SUPPLEMENTARY TABLES

Table S1. Systematic Review Search Terms

Errors	Route of Administration	Compounding	Article Type
([Medication* or drug* or pharmaceutic* or medical or infus*] adj5 error*).mp. OR (Adverse adj5 [event* or reaction*]).mp. OR ([Medication* or drug* or pharmaceutic*] adj5 [contamina* or safety or incompatib*]).mp. OR (Overdos* or over dose*).mp. OR Near miss.mp. OR (incident or incidents or accident*).mp.	parenteral OR intravenous OR catheter* OR infus* OR iv OR intraocular OR intravitreal OR intramuscular OR subcutaneous OR	Compounding OR Compounded OR Reconstitut* OR Admix* OR (Prepar* adj5 (pharmacy or pharmacies or pharmacist or pharmaceutic* or drug* or medication* or ward or wards or nurs* or chemotherapy* or antineoplastic* or cytostatic* or nutrition* or mixture* or solution* or compound or	(clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) (EMBASE limits) OR (Evidence based medicine or consensus development or meta-analysis or outcomes research or "systematic review") (EMBASE limits) OR (Clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or observational study or randomized controlled trial or systematic reviews) (Medline limits) OR (Chart review* or observational or systematic or prospective or cohort or retrospective or controlled study or controlled studies or controlled trial* or cross sectional or evidence based or direct observation* or audit or audits or randomized or blind or blinded or case series).mp. (free text terms)

OR (Steril* or unsteril* or septic or sepsis or aseptic or asepsis).mp. OR ([Healthcare or health care or hospital or bloodstream or blood stream or cross] adj3 infection*).mp. OR patient safety.mp. OR ([Drug or medication* or pharmaceutic*] adj3 [stor*or stability or stable or instability or unstable or expir*).mp. OR ([Wrong* or incorrect* or inappropriate* or error* or inaccura* or deviation*] adj5 (dose* or dosage* or	epidural OR intraosseous OR intraperitoneal OR (ei or im or io or os or ip or iv or pa).fs. use emefd	compounds)).mp.

drug* or medication* or pharmaceutic* or concentration* or diluent* or dilution* or strength* or calculat* or volume or label* or product* or quantit*]).mp.

OR

(Missing label* or "no label*" or "not label*").mp.

OR

particulate*.mp.

Table S2. Patient Burden of Harm

Study	Error Types	Burden of Harm
NCC MERP Medication Error Index Definition of Error Severity		
Fahimi et al. 2007[29]	Wrong drug Wrong label Wrong dose	All observed errors were rated NCC MERP Index Category B ("An error occurred but the error did not reach the patient.")
Rodriguez-Gonzalez et al. 2011[37]	Wrong diluent solution Wrong diluent volume	• Severity was defined according to updated medication errors taxonomy adapted from NCC MERP definitions.[49] • Severity of wrong preparation errors (reconstitution and dilution) were determined to have the potential to cause "no damage."
Sacks et al. 2009[38]	Composite	Severity of errors was defined according to the NCC MERP Index: • 91% of errors did not cause harm (Categories B–D) • 15% of errors were "near misses" (Categories A–B) • 8% of errors contributed to or resulted in temporary harm (Categories E–F) No errors resulted in permanent harm, near-death, or death (Categories G–I)
Clinician Assessment or Expert Panel Definition of Error Severity		
Bertsche et al. 2008[24]	Inadequate aseptic technique	• A multidisciplinary committee for quality assurance established risk scores for medical errors. • Errors were assigned a risk score weighted by potential risk of the drug involved and the characteristics of the error (low risk=0.5, moderate risk=1, high risk=2). • Rates of error by severity were reported for all types of administration combined (IV, oral, and gastric tube), but not

Table S2. Patient Burden of Harm

Study	Error Types	Burden of Harm
		separately.
Moniz et al. 2014[42]	Wrong dose Wrong drug Wrong diluent solution Inadequate aseptic technique Composite	A new workflow was implemented that detected IV preparation errors that would not have been detected previously. These new errors (n = 447) were rated: • Little potential for harm: 62.64% • Potential ADE with moderate harm: 32.66% • Potential ADE with severe harm: 4.70%
Nguyen et al. 2014[43]	Wrong drug Wrong dose Composite	Clinical relevance of each dose with ≥ 1 error was rated on a validated scale ranging from 0 (no harm) to 10 (death) by a panel of healthcare providers, and was categorized as follows: • Minor outcome: 0–2 • Moderate outcome: 3–7 • Severe outcome: 8–10 Moderate and severe outcomes were considered clinically relevant (57.9% to 64.0% of errors across the two study wards).
Niemann et al. 2014[44]	Wrong diluent solution Wrong diluent volume	Clinical relevance of error subcategories was rated by an expert panel on a four-point scale: 1. No clinical relevance

Table S2. Patient Burden of Harm

Study	Error Types	Burden of Harm
	Composite	2. Minor clinical relevance 3. Clinical relevance 4. High clinical relevance The frequency of each level of severity combined oral and IV drug errors.
Seger et al. 2012[39]	Wrong drug	• Severity was rated as life-threatening, severe, significant, or little-to-no harm. • Events with potential for little-to-no harm were not included in the analysis. • There were no potentially life-threatening events, and the remaining events were approximately evenly distributed between significant and serious.
	Wrong concentration	Doses with ±5% to 10% variance were considered to have little to no potential for harm. Those with variance > ±10% were rated serious and potentially harmful.
Westbrook et al. 2011[3]	Wrong drug	• Severity was rated on a scale from 1 ("Incident is likely to have little to no effect on the patient") to 5 ("Incident is likely to lead to death"), with ratings of 1 to 2 considered minor errors and 3 to 5 considered serious errors. • 25.5% of overall errors were rated as serious.
	Wrong diluent solution	• 23.8% of wrong diluent solution errors were rated as serious.
	Wrong diluent volume	• 17.4% of wrong diluent volume errors were rated as serious.
Other Method for Determination of Error Severity		
Crill et al. 2010[27]	Inadequate aseptic technique Bacterial contamination	• Severity of errors was not rated. • Authors noted that no cases of systemic infection arose from syringes which had positive cultures.

Table S2. Patient Burden of Harm

Study	Error Types	Burden of Harm
Ding et al. 2015[46]	Wrong dose	• An error was considered clinically important if it concerned a drug listed in the ISMP list of high alert medications (2008). • 81% of TPN dose errors involved ISMP high alert medications.
	Composite	An error was considered clinically important if it concerned a drug listed in the ISMP list of high alert medications (2008).
Fahimi et al. 2008[30]	Wrong diluent solution Wrong dose	There was no severity rating system, but the authors note that none of the errors identified resulted in adverse effects or major risks to patients.

ADE, adverse drug event; ISMP, Institute for Safe Medication Practices; IV, intravenous; NCC MERP, National Coordinating Council for Medication Error Reporting and Prevention; TPN, total parenteral nutrition.

Table S3. Error Incidence Definitions

Admixture Preparation and Labeling Error Types	Definitions	Study
Component Error		
Wrong Drug	An IV drug was prepared or administered that differed from the one that was prescribed	Anselmi et al. 2007[23] Cousins et al. 2005[26] Moniz et al. 2014[42] Nguyen et al. 2014[43] Ong et al. 2013[35] Seger et al. 2012[39] Westbrook et al. 2011[3]
	An unauthorized IV drug was administered, or an order was changed, that was not found in the patient chart	Fahimi et al. 2007[29]
	An IV drug was prepared or administered with a diluent that was not compatible with drug and volume to achieve the correct concentration	Cousins et al. 2005[26]
Wrong Diluent Solution	An IV drug was prepared with the incorrect diluent based on any of the following: • The manufacturer's instructions • Published drug preparation handbooks • Other internal or external drug preparation guidelines	Fahimi et al. 2008[30] Niemann et al. 2014[44] Ong et al. 2013[35] Westbrook et al. 2011[3]
	An IV drug was prepared with the incorrect diluent	Moniz et al. 2014[42]

	The IV medication was reconstituted or diluted incorrectly according to medication errors taxonomy adapted from NCC MERP definitions [Otero Lopez 2008]	Rodriguez-Gonzalez et al. 2011[37]
	An IV drug was prepared or administered with a missing or incomplete label with respect to drug name, dose, patient name, or preparation time	Cousins et al. 2005[26]
	The administration rate, patient identification, date, or time of infusion was not properly documented	Fahimi et al. 2007[29]
Wrong label	The IV drug label was incomplete with respect to patient, drug, dose, or preparation time, or the opened diluent vials were improperly labeled	Ong et al. 2013[35]
	The syringe label was illegible or missing the drug name, dose, concentration, diluent, patient name, patient location, preparer's initials, countersigned, date, or time	Wheeler et al. 2008[41]
Dose or Calculation Error		
	An incorrect IV drug dose or infusion volume was prepared or administered	Anselmi et al. 2007[23] Cousins et al. 2005[26] Fahimi et al. 2007[29] Hoefel et al. 2006[31]
Wrong Dose		Moniz et al. 2014[42]
	An ingredient deviated > ±10% from the correct volume or concentration, a dose was omitted, or an extra dose was given	Ding et al. 2015[46]
	An IV drug that differed by ±10% of the prescribed dose was prepared	Nguyen et al. 2014[43]
	An incorrect dose or diluent volume was calculated that differed from the manufacturer's instructions or published drug preparation handbooks	Fahimi et al. 2008[30]
	The sampled IV drug preparation deviated by ±20% or more from its intended concentration	Castagne et al. 2011[25]
Wrong Concentration	The sampled IV drug preparation deviated by ≥ ±5% or ≥ ±10% from its intended concentration	Dehmel et al. 2011[28] Masini et al. 2014[34]

	The sampled IV drug preparation deviated by ±10% or more from its intended concentration	Parshuram et al. 2006[36]
	The sampled IV drug preparation deviated by ±5% or more from its intended concentration	Seger et al. 2012[39]
	The concentration of any of the individual components of total parenteral nutrition was calculated incorrectly	Skouroliakou et al. 2005[40]
	An incorrect diluent volume was used	Cousins et al. 2005[26] Hoefel et al. 2006[31]
Wrong Diluent Volume	An IV drug was prepared with an incorrect diluent volume based on any of the following: • The manufacturer's instructions • The corresponding summaries of product characteristics • Published drug preparation handbooks • Other internal or external drug preparation guidelines	Niemann et al. 2014[44] Ong et al. 2013[35] Westbrook et al. 2011[3]
	The IV medication was reconstituted or diluted incorrectly according to medication errors taxonomy adapted from NCC MERP definitions [Otero Lopez 2008]	Rodriguez-Gonzalez et al. 2011[37]
	The total volume of the IV solution was incorrect	Skouroliakou et al. 2005[40]
Aseptic Technique Error		
Inadequate Aseptic Technique	The IV drug was not prepared in accordance with local hygiene guidelines	Bertsche et al. 2008[24]
	Sampling of repackaged syringes resulted in positive bacterial cultures	Crill et al. 2010[27]
	Needles or syringes were left uncapped during IV preparation	Moniz et al. 2014[42]
Bacterial Contamination	Sampling of IV drug preparations resulted in positive bacterial cultures	Crill et al. 2010[27] Khalili et al. 2013[47]

		Macias et al. 2005[32]
Failure to Disinfect Vial	Vial top was not swabbed with alcohol during preparation	Cousins et al. 2005[26] Ong et al. 2013[35]
Improper Hand Hygiene	Hands were not washed, gloves were not worn, or non-sterile gloves were worn during IV drug preparation	Cousins et al. 2005[26] Ong et al. 2013[35]
Composite Error		
Any Admixture or Labeling Error	An IV drug dose was prepared or administered differently from how it was prescribed by the physician in the patient's medical record with regard to: • Wrong patient • Wrong drug • Wrong dose • Omitted dose	Anselmi et al. 2007[23]
	Any of the following IV preparation or administration errors occurred: • Unordered drug • Omitted drug • Wrong dose • Extra dose • Wrong route of administration	Ding et al. 2015[46]
	A drip compounding error of greater than one standard deviation from the calculated value for each component in parenteral nutrition preparations occurred	MacKay et al. 2009[33]
	IV drug preparations in the institution were prepared and verified using an IV workflow manager system. Doses that were	Moniz et al. 2014[42]

reworked or rejected were retrospectively reviewed for errors in: • Preparation • Aseptic technique • Documentation	
Any IV of the following IV preparation or administration errors occurred: • Wrong drug • Wrong dose • Wrong dosage form • Deteriorated drug • Wrong preparation technique • Omission • Unordered drug • Wrong administration technique	Nguyen et al. 2014[43]
At least one deviation from internal or external drug preparation or administration guidelines, corresponding summaries of product characteristics, or manufacturer recommendations occurred during the drug handling processes (eg, preparation, storage, labeling)	Niemann et al. 2014[44]
Documented events in parenteral nutrition preparation or administration: • Dose omission • Extra dose • Prescription or refill delayed • Drug list incorrect • Monitoring error	Sacks et al. 2009[38]

• Unauthorized drug • Inadequate pain management • Wrong events (eg, dose, drug, time, patient) A deviation in handling, preparation, or administration of an IV drug occurred based on: • The manufacturer's instructions • Handbook on Injectable Drugs, 15th ed. • Drug Information Handbook, 19th ed. • American Society of Health-System Pharmacists Drug Information • Oncology Nursing Drug Handbook	Tavakoli-Ardakani et al. 2013[45]

IV, intravenous; NCC MERP, National Coordinating Council for Medication Error Reporting and Prevention

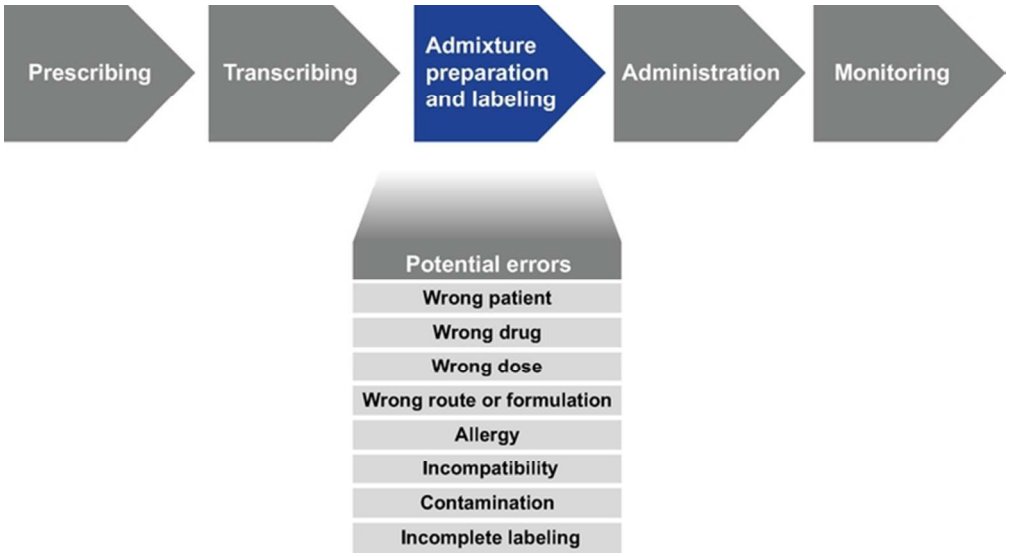

Figure 1 Color

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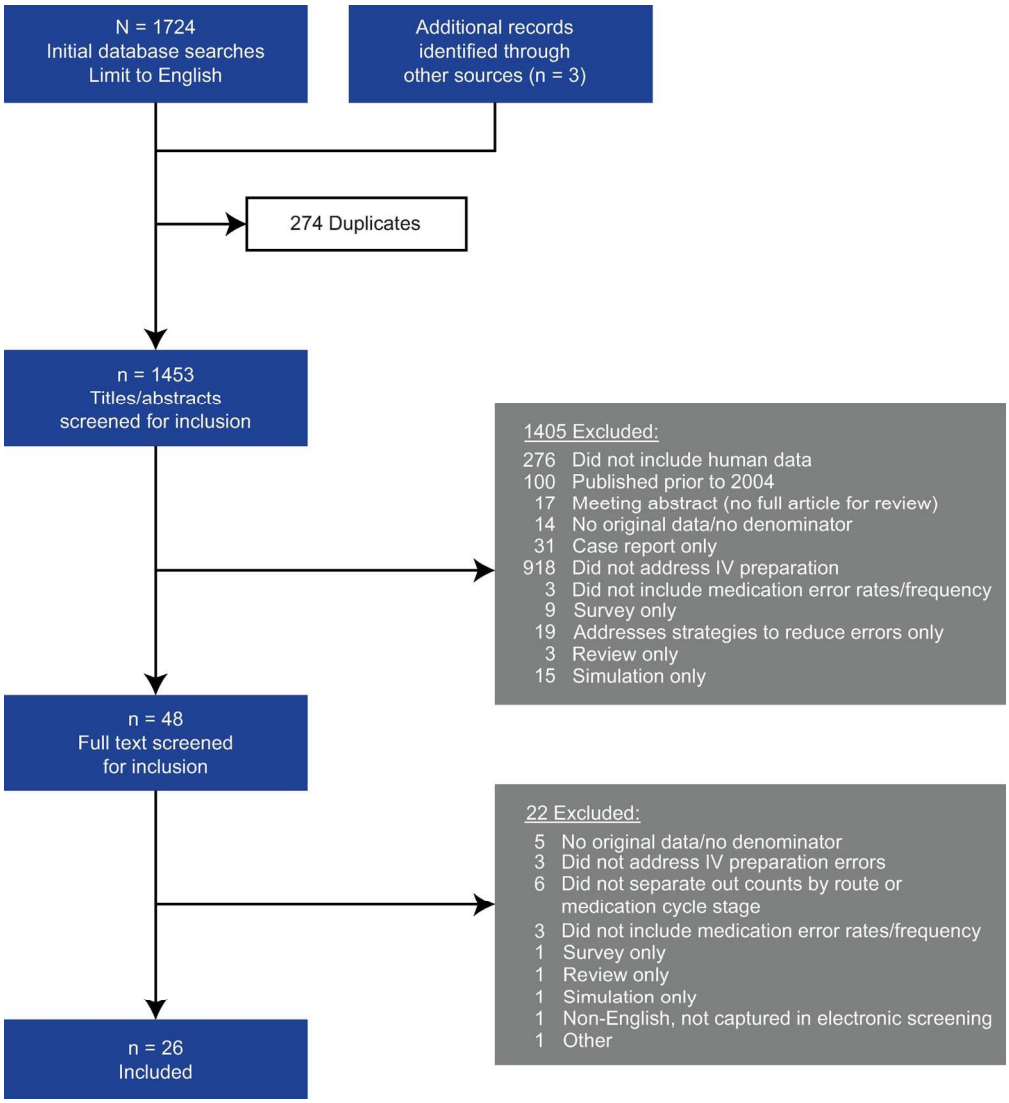

Figure 2 Color

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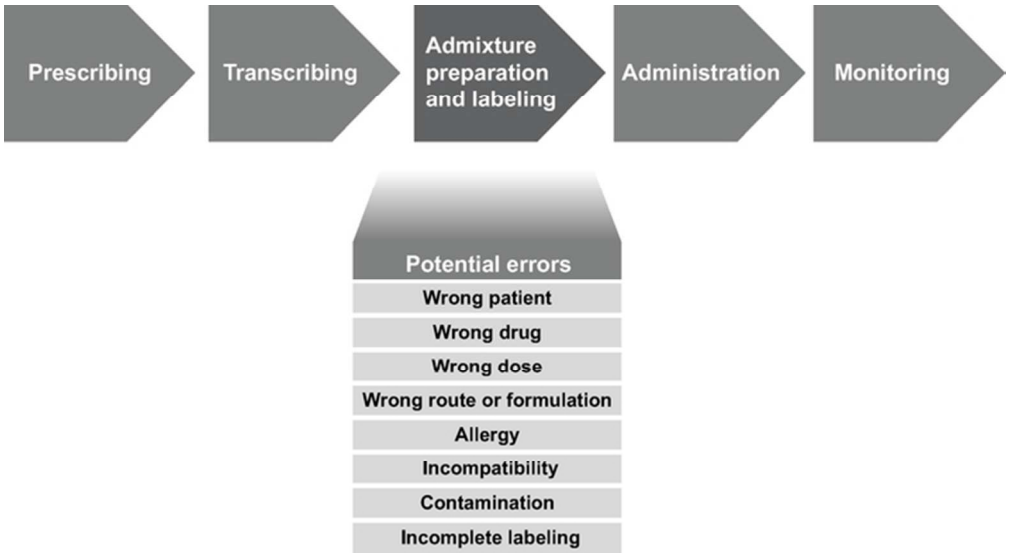

Figure 1 Mono

60x33mm (300 x 300 DPI)

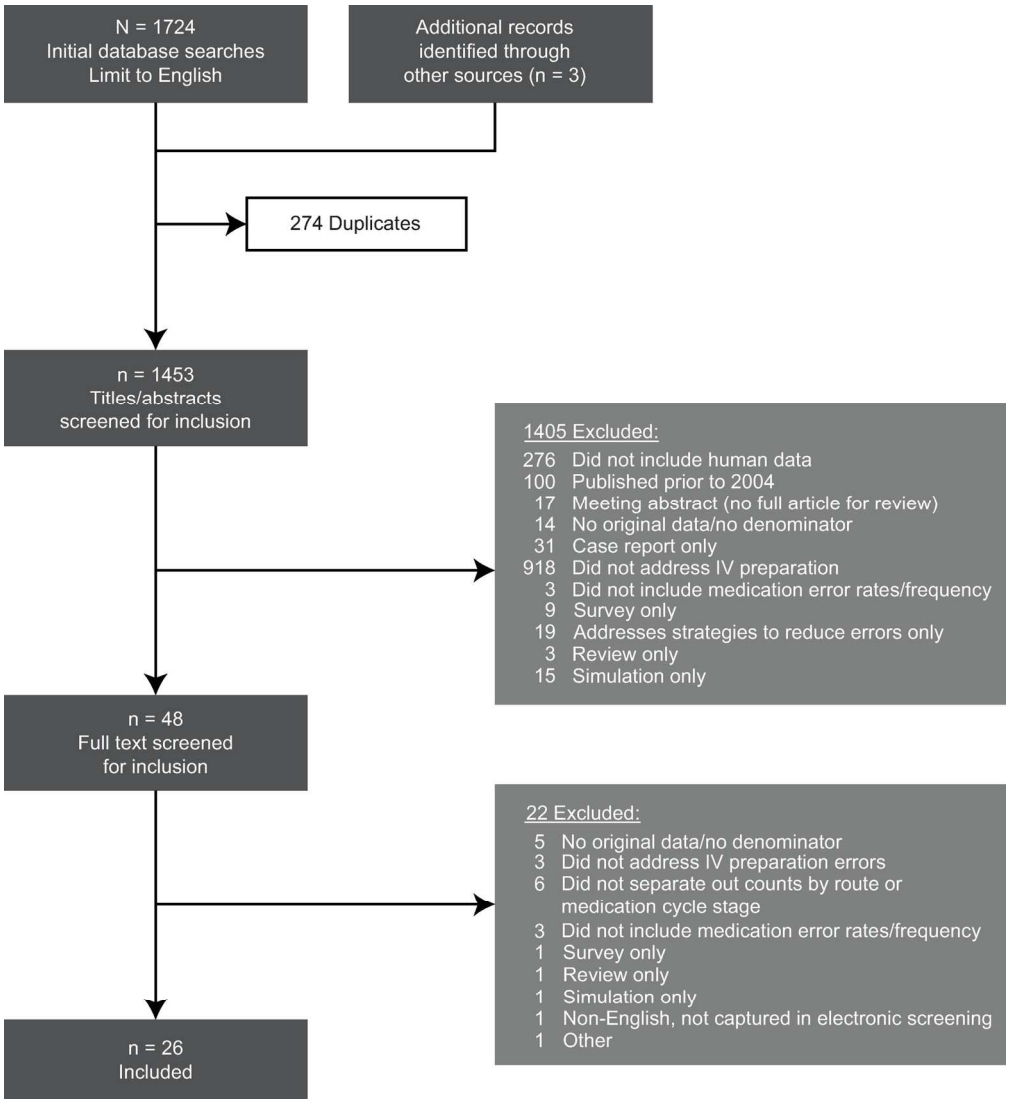

Figure 2 Mono

156x171mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	10
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	40-42
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	30
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	33
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	34
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	35

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Systematic evidence review of rates and burden of harm of intravenous admixture drug preparation errors in healthcare settings

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Systematic evidence review of rates and burden of harm of intravenous admixture drug preparation errors in healthcare settings

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ABSTRACT (300/300)

Objective: To examine published evidence on intravenous (IV) admixture preparation errors (IAPEs) in healthcare settings.

Methods: Searches were conducted in 3 electronic databases (January 2005 to April 2017). Publications reporting rates of IAPEs and error types were reviewed and categorized into the following groups: component errors, dose/calculation errors, aseptic technique errors, and composite errors. The methodological rigor of each study was assessed using the Hawker method.

Results: Of the 34 articles that met inclusion criteria, 28 reported the site of IAPEs: central pharmacies (n = 8), nursing wards (n = 14), both settings (n = 4), and other sites (n = 3). Using the Hawker criteria, 14% of the articles were of good quality, 74% were of fair quality, and 12% were of poor quality. Error types and reported rates varied substantially, including wrong drug (~0% to 4.7%), wrong diluent solution (0% to 49.0%), wrong label (0% to 99.0%), wrong dose (0% to 32.6%), wrong concentration (0.3% to 88.6%), wrong diluent volume (0.06% to 49.0%), and inadequate aseptic technique (0% to 92.7%). Four studies directly compared incidence by preparation site and/or method, finding error incidence to be lower for doses prepared within a central pharmacy versus the nursing ward, and lower for automated preparation versus manual preparation. Although 8 studies (24%) reported ≥1 errors with the potential to cause patient harm, no study directly linked IAPE occurrences to specific adverse patient outcomes.

Conclusions: The available data suggest a need to continue to optimize the IV preparation process, focus on improving preparation workflow, design and implement preventive strategies, train staff on optimal admixture protocols, and implement standardization. Future research should focus on the development of consistent error subtype definitions, standardized reporting

methodology, and reliable, reproducible methods to track and link risk factors with the burden of harm associated with these errors.

Strengths and limitations of this study

- To the authors' knowledge, this is the first systematic review conducted that attempts to categorize intravenous admixture preparation errors (IAPEs) according to both the characteristics of the error and the location and method of intravenous (IV) preparation.
- Although IAPE is a safety concern, its frequency, subtypes, and associated burden of harm are not well understood; thus, the current review presented a thoughtful and valid framework to assess IAPEs within their procedural context.
- This review attempted to include all articles published in English between January 2005 and April 2017 that reported on IAPEs in which healthcare professionals prepared ≥1 dose of IV administered therapy.
- This review is limited by the number of studies identified that reported data on the frequency and/or burden of harm of IAPEs.

INTRODUCTION

Errors in medication preparation and administration can lead to patient harm.[1-3] For example, many preventable adverse events with respect to medication have been linked to errors in dosing (eg, patients receiving higher or lower amounts of medication than intended).[2, 4] The medication use cycle for an intravenous (IV) medication involves multiple steps prior to administration, including prescribing and transcription (paper-based orders), in addition to a number of admixture preparation and labeling steps (**Figure 1**).

Figure 1. Intravenous medication use cycle

An IV admixture preparation error (IAPE) can be considered as any deviation from the specifications involved in the admixture preparation and labeling process. An IAPE is a form of medication error—in other words, a preventable adverse event resulting from inappropriate medication preparation, administration, or use that can lead to patient harm, including death, while the medication is in the control of the healthcare professional, patient, or consumer.[5, 6]

IAPEs can be introduced at multiple points during admixture preparation and labeling. These steps can occur on site at a nursing ward or in a central or satellite pharmacy. IV medication doses are typically prepared (1) manually by nurses, either at the bedside or in a ward-based preparation room, (2) manually by pharmacists and pharmacy technicians in a central or satellite clean room under a laminar-airflow hood, or (3) through the use of pharmacy automation technology, which can be partially or fully automated and may be located in clean rooms or clean compartments within the machine. United States data suggest increasing use of automated technologies aimed at reducing IAPEs, for technologies ranging from robotic chemotherapy compounding devices (0.3% of hospitals) to barcode verification (20% of

hospitals), with higher levels of adoption predominantly within larger hospitals.[7] Delivery of the correct dose of an IV admixture to a patient depends on the careful control of many factors, such as the calculation of a patient-specific dose (eg, based on body weight or organ function), oversight of procedures utilized for admixture preparation, and labeling practices.[4, 8] While research suggests that the highest medication-error rates can be attributed to the prescribing and administration phases of the medication use cycle,[9-11] studies focused on medication preparation practices suggest that the IV admixture preparation and labeling phase pose a significant potential for errors.[9, 12-15] It is unknown what proportion of IAPEs are unreported.

In addition to measuring the incidence of IAPEs, it is also important to understand their impact in terms of burden of harm. Two examples of existing frameworks for categorizing patient harm resulting from medication errors are The Institute for Safe Medication Practices (ISMP) high-alert medication lists and The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Medication Error Index. ISMP publishes information and educational resources for healthcare providers on preventing medication errors, and tracks voluntary medication errors reports. Based on these voluntary error reports, ISMP maintains lists of high-alert medications in outpatient and inpatient settings that have the potential for increased risk of patient harm if used in error.[16] The NCC MERP Medication Error Index groups medication errors into nine possible categories, ranging from non-errors (situations in which errors may occur) to errors resulting in patient death.[17] These categories also include near-miss (near-hit) situations in which an error occurred but did not reach the patient or cause harm. ISMP uses the NCC MERP Medication Error Index in its medication error database.

Much of the prior published research focusing on the prescription or administration of IV therapies has failed to describe or distinguish between errors that arise as a result of the

admixture preparation process versus errors associated with incorrect prescribing or administration.[18-21] With this systematic review, our objective is to identify the incidence of IAPEs (overall and by subtype) reported across institutional healthcare settings and to understand the frequency of error subtypes and associated burden of patient harm attributable to IAPEs as reported in the published literature.

METHODS

Identification of literature and data sources

For the purposes of this review, an IAPE was defined as an error or deviation at any step within the admixture preparation process where the drug container was physically handled or manipulated by a healthcare professional. A broad search strategy was developed to identify all studies (published from January 2005 to September 2015) that mention any type of IAPE in an institutional healthcare setting, which included reports relating to wrong drug, wrong diluent solution, wrong label, wrong dose, wrong concentration, wrong diluent volume, and inadequate aseptic technique. Dose omission errors were considered to be errors related to administration rather than preparation and, thus, were not included as a focus in this study. Near-miss and actual errors (those that did reach patients) were both included. The review was structured based on the PICOS (patients, intervention, comparator, outcomes, and study design) search strategy (**Table 1**).

Table 1. PICOS Search Strategy

Patient/Problem	Incorrect preparation of IV admixtures within an institutional healthcare setting (acute or long-term care) by a licensed healthcare professional (nursing and/or pharmacy staff and/or physician) team member

Intervention	Preparation of an IV admixture
Comparison	Automated versus manual preparation methods (studies were not required to demonstrate both) Central pharmacy versus on-unit (on the nursing ward) preparation location (studies were not required to demonstrate both)
Outcome	Incorrectly prepared or labeled IV admixture, which may or may not have reached a patient: • Wrong drug or diluent • Wrong dose, concentration, or volume • Wrong, inaccurate, or omitted label • Contaminated admixture or failure to follow hygiene or sterility protocols • A combination of the above
Study Types	**Inclusion criteria:** Observational studies for which numerator (number of doses impacted or number of errors) and denominator (number of eligible doses or opportunities for error) are discernible **Exclusion criteria:** Studies in which isolated contamination volumes are reported but for which total batch size is unknown fail to qualify for consideration Error report logs for which number of errors is known but associated number of prepared doses is not also fail to qualify

IV, intravenous; PICOS, patients, intervention, comparator, outcomes, and study design..

Systematic review process

Three electronic databases were searched for relevant literature reporting on IAPE: Ovid MEDLINE, EMBASE, and International Pharmaceutical Abstracts. The initial search was conducted on February 6, 2014, with supplementation on September 4, 2015 to include articles published during the interim. Aggregate results include articles published in English between January 2005 and April 2017 that involved studies in human subjects in which a healthcare professional prepared ≥1 doses of IV administered therapy (medication, including total parenteral nutrition). This date range was selected to include a sufficiently long period to capture the studies of interest, while remaining relevant to current practice in terms of technology and guidelines. Key search terms and limits used in the systematic review are shown in **online supplementary Table S1**. Screenings for relevant literature citations that appeared in the publications were made during the review process to identify any pertinent, additional publications up to April 2017. For this systematic review, references had to meet the

inclusion/exclusion criteria detailed in the next section. Duplicate articles were removed electronically prior to manual review. Titles of the papers and abstracts captured in the electronic search results were screened by 2 reviewers for relevancy according to prespecified criteria. If the titles did not provide sufficient information for screening, the abstract or full-text articles were then reviewed to discern whether the publication met inclusion criteria. All publications that met entry criteria for the review were obtained as full-text articles and then reassessed by the reviewers against the review criteria. The review process was fully compliant with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22]

Inclusion and exclusion criteria

Publications reporting on a randomized, controlled trial, prospective cohort study, observational quality audit, descriptive study, quasi-experimental study, or quality-improvement study were selected for inclusion. Quasi-experimental studies, quality-improvement studies, and descriptive studies were eligible if they included sufficient data on the number of doses prepared. While systematic reviews reporting on these study types were not included, their respective reference lists were reviewed to identify potentially relevant studies. Publications were not limited to a single geographic or physical study location and may have occurred in the hospital or any other institutional or outpatient healthcare setting associated with a hospital.

Publications and studies were included for review if they either reported incidence of IAPE or provided sufficient detail for incidence calculation. These errors included incorrectly dispensed medication as well as near-misses that were caught by the study observer prior to administration. Errors also had to originate with a healthcare professional (eg, nurse or pharmacist). Studies reporting patient or informal caregiver medication errors were not included.

To be included, studies were required to report original data on IAPEs, including a denominator, to allow for incidence calculations.

Articles that described only errors in prescribing, transcription, administration, and monitoring were not included. In addition to all articles that failed to meet the aforementioned inclusion criteria, the following article types were also excluded: conference abstracts, case reports, simulations, and survey findings.

Data extraction

The data extracted from relevant articles for analysis included year of publication, country of origin, study period, patient population, definition of error, IV preparation location (eg, central or satellite pharmacy or nursing ward), care setting (eg, critical care, general nursing ward), type of therapy, method of error detection, and error incidence. Data were extracted and scored independently by 2 separate reviewers, with introduction of a third reviewer in the case of scoring discrepancies, with all differences being resolved by consensus. Each review team included ≥1 pharmacist for professional knowledge and understanding of drug preparation. The methodological rigor of each study was critically appraised and scored using the Hawker method.[23] This appraisal tool is simple and particularly adaptable to literature reviews encompassing varied research methodologies.[24] It employs 9 criteria to evaluate for each study: 1) abstract and title; 2) introduction and aims; 3) method and data; 4) sampling; 5) data analysis; 6) ethics and bias; 7) results; 8) transferability or generalizability; and 9) implications and usefulness. For each criterion, studies were scored as: good (score 4), fair (score 3), poor (score 2), or very poor (score 1). A mean score was then calculated for each study across all 9 criteria, and the overall quality of each study was likewise scored from good to very poor.

For the purposes of this review, IAPEs were grouped into 1 of 4 categories based on the characteristics of the error and the location and method of IV preparation. Component errors were defined as all those that result from selecting an incorrect ingredient (ie, wrong drug or wrong diluent solution), or applying an incorrect, incomplete, or inaccurate label (ie, wrong label) to the admixture. Dose/calculation errors were defined as those involving the use of an incorrect calculation to determine dose and/or diluent amount, or the use of a diluent volume not in accordance with the package insert (ie, wrong dose, wrong concentration, and wrong diluent volume). Aseptic technique errors involved a breakdown in the process designed to minimize the potential for antimicrobial contamination (ie, inadequate aseptic technique, bacterial contamination, failure to disinfect vial, and improper hand hygiene). The category of composite errors was used to describe IAPE rates reported in aggregate, in which the researchers reported an overall rate that included multiple IAPE subtypes. Composite errors included cases in which >1 error or type of error was observed in a single preparation.

This study was registered with the PROSPERO international database of systematic reviews (CRD42014010418) to comply with PRISMA guidelines.

RESULTS

Electronic database searches yielded 2018 English language publications for review. Additional sources (hand searches of publication reference lists) identified another 3 publications for evaluation. After removing duplicates and screening for inclusion and exclusion criteria, 34 articles were included in the final synthesis (**Figure 2**).[3, 25-57] Of the 34 articles, 5 (15%) were rated good quality,[30, 34, 38, 45, 46] 25 (74%) were fair quality,[3, 25-29, 31-33, 36, 37, 39-41, 43, 44, 48, 51-57] and 4 (12%) were poor quality[35, 42, 49, 50] after assessment using the Hawker method. The quality of 1 study (3%) could not be fully scored due to a missing data

table in the available publication.[47] Details of the Hawker analysis for each study are shown in online **supplementary Table S2**.

Figure 2. PRISMA study inclusion flow diagram

Study characteristics

A summary of the study characteristics, in terms of the setting and methodology, described in the 34 publications is presented in **Table 2**. Collectively, the publications reported international data, with studies spanning Africa, North America, South America, Europe, the Eastern Mediterranean region, and the Western Pacific region. Patient populations varied across studies, with both adults and children represented. Studies were conducted mainly in general inpatient or critical care settings, with several in pediatric or hematology units. The majority of publications (21 [62%]) assessed errors in >1 type of IV therapy. Additional individual details for each study are shown in online **supplementary Table S3**.

Table 2. Summary of study characteristics

Study Setting Characteristics	n (%)	Study Methodology Characteristics	n (%)	IV Admixture Preparation Characteristics	n (%)
Geographical region		**Study design**		**Location of IV admixture preparation**	
Europe	13 (38)	Single arm	21 (62)	Nursing ward	13 (38)
Americas	10 (29)	Interventional	8 (24)	Central pharmacy	8 (24)
Western Pacific	6 (18)	Comparative	5 (15)	Not specified	6 (18)
Eastern Mediterranean	4 (12)			Nursing ward and central pharmacy	4 (12)
Africa	1 (3)	**Observational technique**		Nursing ward and operating theater	1 (3)
		Direct observation	17 (50)	Offsite pharmacy	1 (3)
Number of sites		Analysis of final concentration	5 (15)	Obstetric theater	1 (3)
Single-center	28 (82)	Bacterial culture	4 (12)		
2 centers	3 (9)	Cross-checking	3 (9)	**Method of IV admixture preparation**	
3 or more centers	3 (9)	Incident report	3 (9)	Manual	22 (68)
		Chart review	1 (3)	Automated	4 (12)
Patient population		Direct observation and analysis of final concentration	1 (3)	Manual vs automated	4 (12)
Not specified	15 (44)			Not specified	3 (9)
Pediatric patients	10 (29)				
Adult patients	6 (18)	**Measurement of patient impact**		**Types of IV therapies**	
Adult and pediatric patients	3 (9)	Not measured	22 (65)	Multiple	21 (62)
		Clinician assessment or expert panel	6 (18)	Chemotherapy	7 (21)
Care setting		NCC MERP medication error index	3 (9)	Parenteral nutrition or IV lipid emulsion	3 (9)
Critical care*	9 (26)	Other	2 (6)	Antibiotic	1 (3)
General inpatient wards	8 (24)	ISMP high-alert medication	1 (3)	Morphine	1 (3)
Pediatric units	7 (20)			Phenylephrine	1 (3)
Oncology and/or hematology†	6 (18)				
General inpatient and critical care	3 (9)				
Obstetrics	1 (3)				

*Includes intensive care, neonatal intensive care, post-surgical, and neurologic critical care
†Inpatient and/or outpatient
ISMP, Institute for Safe Medication Practices; IV, intravenous; NCC MERP, National Coordination Council for Medication Error Reporting.;

The most common method of detecting errors was direct observation, used in 17 studies (50%),[3, 25, 26, 28, 31-33, 37, 41, 44-48, 52, 55] and 1 study used direct observation and analysis of final IV admixture concentration.[53] Other methods included analysis of final concentration in 5 studies (15%),[27, 30, 36, 38, 51] bacterial culture in 4 studies (12%),[29, 34, 49, 57] cross-checking in three studies (9%),[35, 42, 43] incident reports in 3 studies (9%),[40, 54, 56] and chart review in one study.[50] In several studies using the direct observation method, nurses or pharmacists preparing the IV admixtures consented to participate but were not fully aware of the study aims to avoid influencing their behavior.[18, 39, 45] Eight studies (24%) reported on the accuracy of IV preparation before and after an intervention,[35, 36, 41-43, 45, 46, 52] 5 studies (15%) compared IV admixture preparation locations or methods,[30, 36, 41, 42, 49] and the remaining 21 publications (62%) were single-arm studies.[3, 25-29, 31-34, 37-40, 44, 47, 48, 50, 55-57]

A total of 28 studies reported the IV preparation site. Of those studies, 14 publications (38%) reported preparation on the nursing ward[3, 25, 26, 28, 31-34, 37, 43, 47, 48, 52, 55] and 8 (24%) reported use of central pharmacies.[26, 27, 29, 35, 36, 40, 41, 44, 54] Three studies (12%) compared rates of IAPEs in the nursing ward and a central pharmacy[30, 49, 51] and 1 compared IAPEs in the nursing ward and operating theater.[53] Lastly, 2 studies reported IV preparation at offsite pharmacies[56] and in the obstetric theater,[57] respectively.

While IAPEs were not consistently linked with individual patient outcomes in the studies surveyed, nearly half of the studies attempted to assess the potential for patient impact in some way. Twelve (35%) of the publications included in this review reported on the severity of harm or potential for harm arising from identified IAPEs (see **online supplementary Table S2**), [3, 26, 29, 31, 32, 39-41, 44-46, 48] 8 (67%) of which reported ≥1 errors to result in various degrees

of harm,[3, 26, 40, 41, 44-46, 48] and 4 (33%) having reported no errors to have resulted in adverse outcomes or to have presented a major patient risk.[29, 31, 32, 39]

Of the 12 studies that reported on burden of harm, 3 (25%) used the NCC MERP medication error index[17] to score identified errors;[31, 39, 40] while 6 studies (50%) relied on clinician assessment or an expert panel for determination of error severity.[3, 26, 41, 44-46] Among the 6 studies that used clinician assessment or an expert panel, 2 of the study teams (Niemann et al[46] and Nguyen et al[45]) assessed errors based on clinical relevance rather than assigning a score based on patient harm or potential for harm. The remaining 3 studies each took a different approach to estimating patient harm.[29, 32, 48] Ding and colleagues[48] were the only authors to record whether the error was associated with a drug found on the ISMP list of high-alert medications. Crill and colleagues[29] did not have a system for rating error severity but did note that no contamination errors resulted in patient infections. Lastly, the 2008 study by Fahimi and colleagues[32] did not describe a specific system for rating error severity, but noted that none of the errors identified resulted in adverse events or major risks to patients. Further detail on how each study assessed patient burden of harm is shown in **online supplementary Table S4.**

Categorization and incidence of IAPEs

Errors identified in the selected studies were grouped into 4 broad categories: component errors, dose/calculation errors, aseptic technique errors, and composite errors, as detailed in the Methods section. Errors of the same subtype were frequently defined slightly differently among studies; full descriptions of the error subtype definitions are shown in **online supplementary Table S5**. Incidence values for error subtypes are presented in **Table 3**.

Table 3. Summary of Reported IAPE Incidence by Error Subtype

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
Anselmi et al. 2007[25]	Numerator: errors (including near-misses) Denominator: Doses prepared	Site 1: 0/804 Site 2: 0/100 Site 3: 1/487			Site 1: 8/804 Site 2: 2/100 Site 3: 36/487							Across all sites: 118/1391
	Incidence:	**0.00%–0.20%**			**0.90%–7.40%**							**8.48%**
Aruna et al. 2015[50]	Numerator: errors Denominator: cases											19/225
	Incidence:											**8.40%**
Bertsche et al. 2008[26]	Numerator: events Denominator: drug-handling processes							218/315				
	Incidence:							**69.20%**				
Campino et al. 2016[51]	Numerator: Errors Denominator: Doses prepared				NICUs: 6/444 Central pharmacy: 0/60			NICUs: 243/444 Central pharmacy: 23/60				
	Incidence:				**0.00%–1.35%**			**38.33%–54.73%**				
Castagne et al. 2011[27]	Numerator: errors (102 near-misses; 544 errors) Denominator: doses prepared					646/7382						
	Incidence:					**8.80%**						
Cousins et al. 2005[28]	Numerator: errors (not including near-misses)	UK: 0/273 GER: 0/425 FR: 0/100	UK: 2/273 GER: 208/425 FR:	UK: 118/273 GER: 421/425	UK: 1/273 GER: 7/425 FR: 5/100		13 /798 total			UK: 295/299 GER: 245/425	UK: 299/299 GER: 403/425	

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
	Denominator: doses prepared		18/100	FR: 20/100						FR: 4/100	FR: 9/100	
	Incidence:	**0.00%–0.00%**	**1.00%–49.00%**	**20.00%–99.00%**	**1.00%–5.00%**		**2.00%**			**4.00%–99.00%**	**9.00%–100%**	
Crill et al. 2010[29]*	Numerator: positive bacterial cultures Denominator: syringes prepared							3/90	3/90			
	Incidence:							**3.30%**	**3.30%**			
Dehmel et al. 2011[30]†	Numerator: errors Denominator: doses prepared					±5% deviation: 16/100 ±10% Deviation: 5/100						
	Incidence:					**5.00%–16.00%**						
Dehmel et al. 2011[30]‡	Numerator: errors Denominator: doses prepared					±5% deviation: 53/100 ±10% deviation: 22/100						
	Incidence:					**22.00%–53.00%**						
Ding et al. 2015[48]§	Numerator: errors Denominator: TOE (ordered and unordered doses)				50/593							54/593
	Incidence:				**8.43%**							**9.10%**
Fahimi et al. 2007[31]	Numerator: errors (including near-misses) Denominator: doses administered	2/43		4/43	14/43							
	Incidence:	**4.65%**		**9.30%**	**32.60%**							
Fahimi et al. 2008[32]¶	Numerator: errors (including near-misses) Denominator: doses prepared		49/524		38/524							

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
Helder et al. 2016[52]	**Incidence:**		**9.35%**		**7.25%**							
	Numerator: Errors Denominator: Doses prepared							177/191		98/191		
	Incidence:							**92.67%**		**51.31%**		
Hoefel et al. 2006[33]	Numerator: errors Denominator: doses administered				14/99		6/99					
	Incidence:				**14.10%**		**6.10%**					
Khalili et al. 2013[49]	Numerator: positive bacterial cultures Denominator: doses prepared								Nursing ward: 1/92 Central pharmacy: 0/17			
	Incidence:								**0.00–1.10%**			
Macias et al. 2005[34][‖]	Numerator: positive bacterial cultures Denominator: doses prepared								1/51			
	Incidence:								**1.45%**			
MacKay et al. 2009[35]**	Numerator: errors Denominator: 1000 doses prepared											0.66/1000
	Incidence:											**0.07%**
Masini et al. 2014[36][††]	Numerator: errors Denominator: doses prepared					5% relative error: 1/333 10% relative error: 4/333						
	Incidence:					**0.30%–1.20%**						
Moniz et al. 2014[44][‡‡]	Numerator: errors Denominator: doses prepared	8/ 425,683	3/ 425,683		857/ 425,683			11/ 425,683				2883/ 425,683

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
Nguyen et al. 2014[45][§§]	**Incidence:**	**~0.00%**	**~0.00%**		**0.20%**			**~0.00%**				**0.68%**
	Numerator: errors (including near-misses) Denominator: TOE (administered and omitted doses)	ICU: 1/236 PSU: 1/280			ICU: 27/236 PSU: 17/280							ICU: 159/236 PSU: 204/280
	Incidence:	**0.36%–0.42%**			**6.10%–11.40%**							**67.3%–72.90%**
Niemann et al. 2015[46]	Numerator: errors Denominator: drug-handling processes		38/233				115/233					138/233
	Incidence:		**16.00%**				**49.00%**					**59.00%**
Ong et al. 2013[37]	Numerator: errors (including near-misses) Denominator: doses administered	1/349	1/349	11/349			61/349			307/349	81/349	
	Incidence:	**0.28%**	**0.28%**	**3.20%**			**17.50%**			**88.00%**	**23.20%**	
Parshuram et al. 2006[38]	Numerator: errors Denominator: infusion bags prepared					24/78						
	Incidence:					**31.00%**						
Rashed et al. 2016[53]	Numerator: Errors (including near misses) Denominator: Doses prepared		Theater: 0/98 Nursing ward: 1/55			Theater: 31/35 Nursing ward: 17/43		Theater: 25/98 Nursing ward: 1/55		Theater: 98/98 Nursing ward: 55/55	Theater: 82/98 Nursing ward: 0/98	
	Incidence:		**0.00%–1.81%**			**39.53%–88.57%**		**1.81%–15.31%**		**100%–100%**	**0.00%–83.67%**	
Reece et al. 2016[54]	Numerator: Errors Denominator: Doses prepared:	Self-reported: 1/15,843 Software reported: 52/51,037	Self-reported: 4/15,843 Software reported: 5/51,037		Self-reported: 7/15,843 Software reported: 797/		Self-reported: 4/15,843 Software reported: 37/					

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
					51,037		51,037					
	Incidence:	**~0.00–0.01%**	**0.01%–0.03%**		**0.04%–1.56%**		**0.03%–0.07%**					
Rodriguez-Gonzalez et al. 2012[39]¶¶	Numerator: errors (including near-misses) Denominator: TOE (observed administrations plus omitted doses)		8/402				32/402					
	Incidence:		**1.99%**				**7.96%**					
Sacks et al. 2009[40]	Numerator: errors Denominator: doses prescribed											18/4730
	Incidence											**0.38%**
Seger et al. 2012[41]‖	Numerator: errors Denominator: doses prepared	3/1421				23/184						
	Incidence:	**0.21%**				**12.50%**						
Skouroliakou et al. 2005[42]	Numerator: errors Denominator: solutions prepared					20/941	8/941					
	Incidence:					**2.13%**	**0.85%**					
Tavakoli-Ardakani et al. 2013[47]†††	Numerator: errors Denominator: TOE											2705/8322
	Incidence:											**32.50%**
Terkola et al. 2017[56]	Numerator: Errors Denominator: Preparations					59,890/759,060						
	Incidence:					**7.89%**						

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
van den Heever et al. 2016[57]	Numerator: Errors Denominator: Sampled preparations			0–101/110					7/110			
	Incidence:			**0.00–91.81%**					**6.36%**			
Westbrook et al. 2011[3]	Numerator: errors (including near-misses) Denominator: doses administered	1/568	21/568				121/568					
	Incidence:	**0.18%**	**3.70%**				**21.30%**					
Wheeler et al. 2008[43]	Numerator: errors Denominator: syringes prepared			88/149								
	Incidence:			**59.10%**								
Yin et al. 2016[55]* **	Numerator: Doses with ≥1 errors Denominator: TOE (observed administrations plus omitted doses)	0/122		15/122	1/122		14/122					69/122
	Incidence:	**0.00%**		**12.30%**	**0.82%**		**11.50%**					**56.66%**

* Crill et al. 2010[29]. Authors speculate that contamination arose during preparation, but note that it may also have occurred during or after administration.
† Dehmel et al. 2011[30]. Results presented for automated preparation in the centralized pharmacy.
‡ Dehmel et al. 2011[30]. Results presented for manual preparation in the nursing ward.
§ Ding et al. 2015[48]. Wrong dose error rate combines wrong dose, omission, and extra dose.
¶ Fahimi et al. 2008[32]. Wrong dose and wrong diluent volume were combined into 1 value in the original article.
‖ Macias et al. 2005[34]. This study was designed to observe a sepsis outbreak. Only baseline (pre-outbreak) data are presented in this table.
** MacKay et al. 2009[35]. This study tested automation as an intervention. Only baseline data is presented in this table.
†† Masini et al. 2014[36]. Results presented for manual preparation only.
‡‡Moniz et al. 2014[44]. Wrong volume of drug/diluent (detectable by previous practices), wrong drug volume (not detectable by previous practices), and wrong diluent volume (not detectable by previous practices) are combined in this table as wrong dose.
§§ Nguyen et al. 2014[45]. This was an interventional study. Only baseline data is presented in this table.
¶¶ Rodriguez-Gonzalez et al. 2012[39]. Errors were defined as "wrong reconstitution (volume, fluid)," which is reported in this table as wrong diluent solution, and "wrong dilution (volume, fluid)," which is reported in this table as wrong diluent volume.

‖ Seger et al. 2012[41]. Results presented for manual preparation only. Wrong dose and wrong diluent were reported as a combined value in the original article.
*** Yin et al. 2016[55]. One preparation out of 122 was subcutaneous rather than IV. Denominator for concentration errors is IV preparations only.
††† Tavakoli-Ardakani et al. 2013[47]. This study reported that additional data was collected by error subcategory; however, these data are not present in the available publication.
Unless otherwise noted, all data reported from interventional studies are from the baseline period only.

FR, France; GER, Germany; ICU, intensive care unit; PSU, post-surgical unit; TOE, total opportunities for error; UK, United Kingdom

The error subtype of wrong drug selection was infrequent,[3, 25, 28, 31, 37, 41, 44, 45, 54, 55] with the highest reported rate of 4.7% of total doses.[31] Selection of a wrong diluent solution was reported to have occurred in 9 of 34 publications (26%), with results varying across studies (~0% to 49.0%).[3, 28, 32, 37, 39, 44, 46, 53, 54] Of note, the multicenter, multinational study by Cousins et al[28] reported that 1.0% to 49.0% of doses administered had been prepared with an incorrect diluent across all study sites. This range is wider than that of the other included studies (0% to 16.0%). Labeling errors were reported in 6 publications (18%), with reported incidence varying substantially, ranging from 0% to 99.0% (20.0% to 99.0% within the study by Cousins et al[28] and 0% to 91.8% in the study by van den Heever et al study[57]).[28, 31, 37, 43, 55, 57]

Eleven publications (32%) captured incidence of wrong dose, and while most of these studies reported incidence rates below 10%,[25, 28, 32, 33, 44, 45, 48, 51, 54, 55] 1 study did report an incidence rate over 32%.[31] Wrong drug concentration errors were reported in 10 publications (29%), with error incidence per total number of IV doses prepared ranging from 0.3% to 88.6%.[27, 30, 36, 38, 41, 42, 51, 53, 55, 56] While some studies defined a concentration error based on a threshold of a 5%[30, 36, 41] or 10%[30, 36, 38, 51, 55] deviation between the prepared dose and the ideal dose, the study by Castagne et al used a higher threshold of 20%.[27]

Eight studies (24%) reported errors pertaining to wrong diluent volume,[3, 28, 33, 37, 39, 42, 46, 54] with half explicitly defining this error subgroup as any deviation from manufacturer or accepted institutional guidelines for IV preparation.[3, 37, 39, 46] The highest-reported error rate (49.0%) was identified by Niemann and colleagues,[46] while the lowest-reported incidence (0.6%) was from a study by Reece et al.[54]

Reported challenges with aseptic technique included general aseptic technique deviations, bacterial contamination, failure to disinfect the vial, and improper hand hygiene. In studies that reported general inadequate aseptic technique deviations, 3 studies reported incidence rates below 5% (range: 0% to 3.3%)[29, 44, 53]; however, the study by Bertsche and colleagues[26] reported an incidence rate of just under 70% and findings from Helder et al indicated a 92.7% nonadherence rate to hygiene protocols.[52] The variation in incidence rates presented may be the result of differences in error definitions, as Bertsche and colleagues assessed aseptic technique deviations as any procedural deviation from local hygiene guidelines[26] and a study by Helder et al required all 5 steps of the hygiene protocol to be followed.[52] The other studies defined aseptic technique errors either based on bacterial cultures[29, 34] or report of syringes left uncapped during the preparation process.[44]

Bacterial contamination errors were reported in 4 studies, with all reporting incidence under 7% (**Table 3**).[29, 34, 49, 57] Four additional studies report error incidence for both failure to disinfect the vial[28, 37, 52, 53] and improper hand hygiene.[28, 37, 53] In particular, the study by Cousins and colleagues[28] presents a wide range of incidence across aseptic technique subtypes (**Table 3**). The study by Cousins et al[28] presented data from 3 separate institutions located in France, Germany, and the United Kingdom, with the incidence of aseptic technique errors from the French institution found to be dramatically lower (4.0% for vial disinfection and 9.0% for hand washing). Of note, the authors attribute this difference to the French institution having undergone a recent update to its aseptic preparation methods protocol due to a prior outbreak of Legionnaire's disease within the facility.[28]

Ten (29%) studies reported an overall incidence of IAPEs that combined multiple error subtypes.[25, 35, 40, 44-48, 50, 55] These studies have diverse error definitions and error detection methods; thus, the error incidence ranges widely (0.07% to 72.9%).

DISCUSSION

This systematic review found that IAPEs are ubiquitous across countries and hospital locations, and that the types of errors observed and reported are diverse. Reported error incidence was found to vary widely not only between settings (central pharmacies or nursing wards) but also within these settings across studies. Variability in error detection methods and definitions applied may contribute to the variation in error rates reported across studies.

This review identified studies conducted in Europe, North America, South America, Asia, and Africa. While different regions, countries, and even individual institutions are likely to have somewhat different standards and practices for IV admixture preparation, differences in methods and terms applied for data collection did not seem to vary any greater between countries than within a single country. In theory, variation among institutions within the same country has the potential to be larger than variation among countries, as local practices may be more flexible than nationally adopted standards. ISMP noted in its 2011 Guidelines for the Safe Preparation of Sterile Compounds that IV admixture preparation practices are complex, and documentation of errors varies widely across the United States.[58] This highlights an important need for national and international consensuses on defining and identifying IAPEs to fully understand the global patient burden.

Some evidence indicates the effect of location and method of IV admixture preparation on the incidence of errors. In particular, error rates appear to be lower when IV preparation takes

place in central pharmacy settings compared with nursing wards, and lower with automated versus manual preparation. Among studies meeting the inclusion criteria for this systematic review, Dehmel and colleagues[30] and Khalili et al[49] directly compared error rates identified from a central pharmacy to those from a nursing ward using consistent IAPE definitions across settings. The study by Dehmel et al reported a markedly higher rate of wrong concentration errors using manual preparation in a nursing ward when compared with automated preparation in a central pharmacy (53% vs 16%, respectively).[30] Khalili and colleagues reported a low rate of bacterial contamination (1.1%) in admixtures prepared on nursing wards, with no instances of contamination in admixtures prepared in central pharmacies, despite use of manual preparation techniques in each setting.[49] Caution should be taken in generalizing this finding, given the limited sample size of 17 preparations in the central pharmacy and 97 on the nursing ward.[49] Thus, while it appears that moving IV admixture preparation away from the site of care and using automated technologies may reduce IAPEs, further empirical studies are required to substantiate this hypothesis.

In the present systematic review of IAPEs, a patchwork of data emerged from the relevant available literature, in part because no single study design or observational technique is ideal for capturing all the aspects of IV admixture preparation that could result in an error. The majority of studies relied on direct observation of the IV admixture preparation process by a trained observer, while other studies used bacterial culture, measurement of the final admixture concentration, incident reports, and cross-checking against a checklist, computed calculation, or other benchmarks. However, certain error subtypes naturally lent themselves to a specific observational technique, such as bacterial culture for assessing bacterial contamination,

laboratory testing for concentration errors, and direct observation for aseptic technique deviations.

The framework used for categorizing IAPEs in this review was developed to facilitate the aggregation of data collected across studies. While inconsistency across reported error definitions precluded additional quantitative aggregation, we hope the classification system used herein is informative to researchers designing future studies, and may help to facilitate more effective standardization of error reporting going forward.

Within IAPE subtypes, the method of error calculation varied in some cases, which impacted the ability to generalize results across studies. The majority of studies reported the incidence as errors per doses prescribed, prepared, or administered. However, 5 (15%) studies reported errors per total opportunities for error[39, 45, 47, 48, 55] and 2 (6%) studies reported errors per total drug-handling processes.[26, 46] While using total opportunities for error or drug-handling processes may be insightful for those wishing to understand and optimize the IV medication use cycle from the user perspective, errors per dose may be a more useful measurement for researchers interested in patient impact and outcomes.

Error definitions were also variable within some error subtypes. For instance, thresholds for determining concentration errors ranged from ±5% variance from the label specification to as high as ±20% variance.[27, 30, 36, 38, 41, 42, 51, 53, 55, 56] Studies reporting IAPE incidence based on a composite of IAPE subtypes were often composed of common elements (eg, wrong drug, wrong concentration), but were sufficiently different that they could not be directly compared. This finding exposes a need for a standardized taxonomy of error subtypes that can be used across a variety of research settings and countries to facilitate meaningful comparisons.

Other factors that may impact error incidence are circumstances, such as either a recent training or sentinel event as described by a study by Cousins et al,[28] when commenting on proportionally lower aseptic technique deviations observed in the French study site. It was suggested that this finding may be attributed to recent staff training and updated guidelines in the French institution included in the study, prompted by a recent outbreak of Legionnaire's disease at that site. This highlights the impact of staff training not only as a source of potential regional or institutional error variation, but also as a means of reducing error rates. Given the short duration between staff training and study implementation, the long-term sustainability of error reduction potentially gained by staff training in the study by Cousins et al was unclear.

In addition to heterogeneous error incidence results, the articles captured in this systematic review used a variety of approaches to measuring the potential burden of patient harm. Several studies used the existing NCC MERP error index[17] to rate and score errors, and the majority of other studies relied on either local clinician opinion or expert panel. As a result, there is a high degree of variability in terms of how the errors are scored and how potential for patient risk is attributed.

Of the 26 studies included in this review, 12 (35%) provided estimates or general assessments for potentially attributable patient harm or clinical relevance for IAPEs,[3, 26, 29, 31, 32, 39-41, 44-46, 48]. Effective and standardized traceability measures are required to link a defect in the admixture process that occurs early within the medication use cycle with later negative patient outcomes. Given the separation in time and physical location between admixture preparation and potential patient physical adverse response, it can be challenging to link potential negative patient outcomes to the admixture/compounding process where unrecognized potential

errors may exist.[12] There is a need for robust study designs that allow for the assessment of the association between specific errors incidences and patient outcomes.

Several limitations were present in this systematic review. Our search strategy targeted the broad medical literature, but inclusion of additional databases, such as the Cumulative Index of Nursing and Allied Health Literature, may have added nursing publications relevant to this topic. While the quality of publications was generally fair, only 5 studies (15%) were deemed to be of good quality in terms of methodology and reporting.[30, 34, 38, 45, 46] Furthermore, the Hawker method of quality ascertainment is generic and may not be best suited to capturing the unique challenges of this research topic. Drawing comparisons between the studies remains difficult due to substantial variations in error definitions. As a result, meta-analysis of the current IAPE literature was not considered appropriate. Lastly, in the majority of studies, documentation of error severity and associated burden of harm was not sufficient to allow for a thorough evaluation of the impact on patient care or the consequences for healthcare facilities.

CONCLUSIONS

This systematic review is the first to categorize IAPEs according to the characteristics of the error and the location and method of IV preparation. It is our hope that future studies may use these categorizations to provide a meaningful framework to assess IAPEs within their procedural context. With improved standardization of IAPE definitions, grouping error subtypes as we have done may facilitate an improved understanding of where errors happen within the IV preparation process and devising solutions to help eradicate them. There is a clear potential burden of harm for patients resulting from IAPEs, and thus a need to continue to optimize the IV preparation process, focusing on improving preparation workflow, designing and implementing preventive strategies, staff training, and implementing process standardization where possible. Future

research should focus on the development of consistent error subtype definitions and a standardized reporting methodology as well as reliable and reproducible methods to track and link risk factors and the burden of harm associated with these errors.

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Data Sharing Statement

As the research presented is a systematic literature review of published data, no additional unpublished data are available.

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Contributors

NH: Concept/design, data analysis/interpretation, critical revision of article, approval of article.

IB: Data interpretation, critical revision of article, approval of article.

T H-T: Concept/design, data interpretation, critical revision of article, approval of article.

PT: Concept/design, data interpretation, critical revision of article, approval of article.

Competing Interests

NH is a former employee and stockholder of Baxter Healthcare Corporation.

IB is an employee and stockholder of Baxter Healthcare Corporation.

T H-T has no relevant competing interests to disclose.

PT is currently under contract to perform other work for Baxter Healthcare Corporation that is unrelated to the current manuscript.

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FIGURE TITLES AND LEGENDS

Figure 1. Intravenous Medication Use Cycle

Figure 2. PRISMA study inclusion flow diagram

IV, intravenous; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

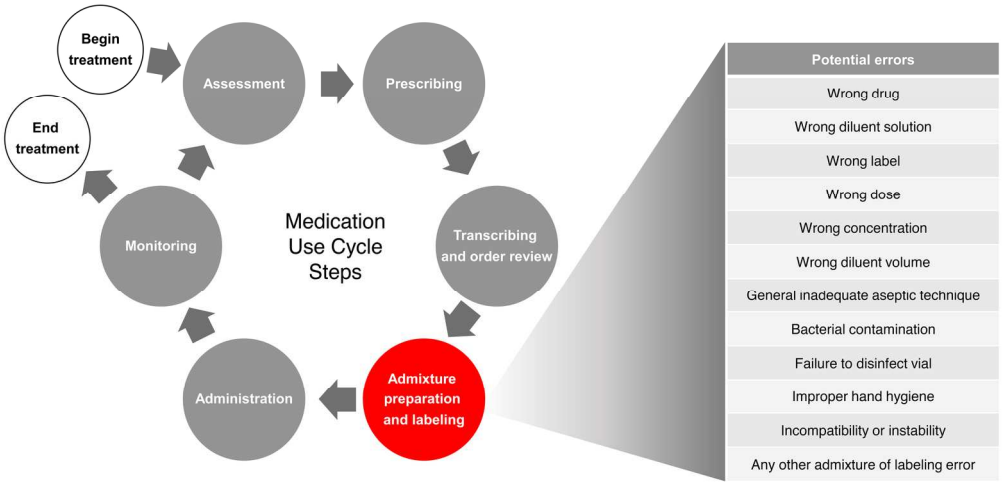

Figure 1. Intravenous medication use cycle

86x41mm (600 x 600 DPI)

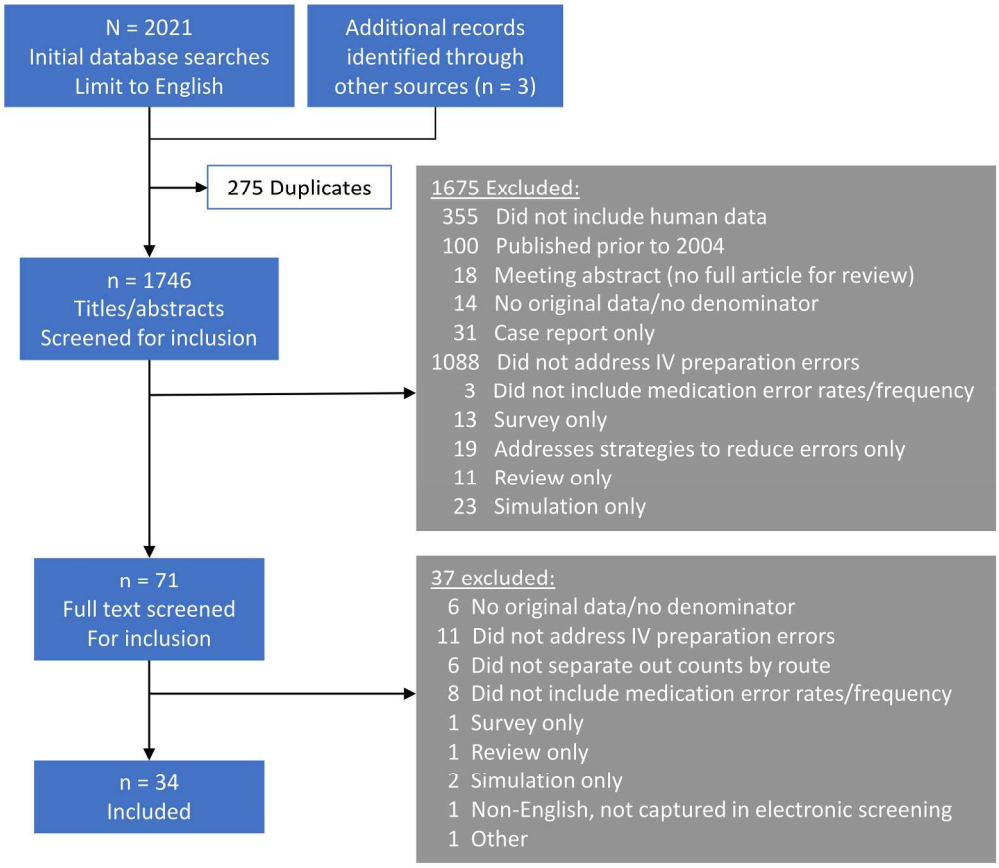

Figure 2. PRISMA study inclusion flow diagram

110x96mm (600 x 600 DPI)

ONLINE SUPPLEMENTARY TABLES

Table S1. Systematic Review Search Terms

Errors	Route of Administration	Compounding	Article Type
([Medication* or drug* or pharmaceutic* or medical or infus*] adj5 error*).mp. OR (Adverse adj5 [event* or reaction*]).mp. OR ([Medication* or drug* or pharmaceutic*] adj5 [contamina* or safety or incompatib*]).mp. OR (Overdos* or over dose*).mp. OR Near miss.mp. OR (incident or incidents or accident*).mp. OR (Steril* or unsteril* or septic or sepsis or aseptic or asepsis).mp. OR ([Healthcare or health care or hospital or bloodstream or blood stream or cross] adj3 infection*).mp. OR patient safety.mp. OR ([Drug or medication* or pharmaceutic*] adj3 [stor*or stability or stable or instability or unstable or expir*).mp. OR ([Wrong* or incorrect* or inappropriate* or error* or	parenteral OR intravenous OR catheter* OR infus* OR iv OR intraocular OR intravitreal OR intramuscular OR subcutaneous OR epidural OR intraosseous OR intraperitoneal OR (ei or im or io or os or ip or iv or pa).fs. use emefd	Compounding OR Compounded OR Reconstitut* OR Admix* OR (Prepar* adj5 (pharmacy or pharmacies or pharmacist or pharmaceutic* or drug* or medication* or ward or wards or nurs* or chemotherapy* or antineoplastic* or cytostatic* or nutrition* or mixture* or solution* or compound or compounds)).mp.	(clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) (EMBASE limits) OR (Evidence based medicine or consensus development or meta-analysis or outcomes research or "systematic review") (EMBASE limits) OR (Clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or observational study or randomized controlled trial or systematic reviews) (Medline limits) OR (Chart review* or observational or systematic or prospective or cohort or retrospective or controlled study or controlled studies or controlled trial* or cross sectional or evidence based or direct observation* or audit or audits or randomized or blind or blinded or case series).mp. (free text terms)

inaccura* or deviation*] adj5 (dose* or dosage* or drug* or medication* or pharmaceutic* or concentration* or diluent* or dilution* or strength* or calculat* or volume or label* or product* or quantit*]).mp. OR (Missing label* or "no label*" or "not label*").mp. OR particulate*.mp.	

Table S2. Details of Hawker Analysis

	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalizability	Implications and Usefulness	Average Score	Overall Quality
Anselmi et al. 2007[1]	2	2	1	3	1	2	2	3	3	**2**	**Fair**
Aruna et al. 2015[2]	2	3	3	3	2	3	3	3	4	**3**	**Poor**
Bertsche et al. 2008[3]	3	3	3	2	1	2	2	2	2	**2**	**Fair**
Campino et al. 2016[4]	2	1	1	1	1	3	1	2	2	**2**	**Fair**
Castagne et al. 2011[5]	2	1	1	3	4	4	1	3	1	**2**	**Fair**
Cousins et al. 2005[6]	1	2	1	3	3	2	2	3	2	**2**	**Fair**
Crill et al. 2010[7]	1	1	1	2	1	1	2	1	2	**2**	**Fair**
Dehmel et al. 2011[8]	1	1	2	3	1	1	2	3	2	**1**	**Good**
Ding et al. 2015[9]	1	2	1	1	2	2	1	3	1	**2**	**Fair**
Fahimi et al. 2007[10]	2	2	2	3	4	2	3	3	1	**2**	**Fair**
Fahimi et al. 2008[11]	1	1	2	3	3	2	2	3	1	**2**	**Fair**
Helder et al. 2016[12]	3	2	1	1	2	2	1	2	3	**2**	**Fair**
Hoefel et al. 2006[13]	2	2	3	1	2	1	2	2	2	**2**	**Fair**

Khalili et al. 2013[14]	2	2	2	3	3	4	2	3	3	**3**	**Poor**
Macias et al 2005[15]	2	1	1	1	1	2	1	1	3	**1**	**Good**
MacKay et al. 2009[16]	2	2	3	4	4	4	3	3	2	**3**	**Poor**
Masini et al. 2014[17]	2	2	3	2	1	4	2	2	3	**2**	**Fair**
Moniz et al. 2014[18]	1	1	2	3	3	4	2	3	3	**2**	**Fair**
Nguyen et al. 2014[19]	1	1	1	2	1	2	1	2	1	**1**	**Good**
Niemann et al. 2015[20]	1	1	1	1	1	2	2	2	2	**1**	**Good**
Ong et al. 2013[21]	2	2	2	3	1	4	2	3	2	**2**	**Fair**
Parshuram et al. 2006[22]	2	2	1	1	1	2	1	2	2	**1**	**Good**
Rashed et al. 2016[23]	1	2	2	3	2	3	1	3	2	**2**	**Fair**
Reece et al. 2016[24]	1	1	1	2	3	3	1	2	2	**2**	**Fair**
Rodriguez-Gonzalez et al. 2012[25]	2	1	1	3	2	2	2	3	2	**2**	**Fair**
Sacks et al. 2009[26]	1	1	1	3	3	1	2	3	2	**2**	**Fair**
Seger et al. 2012[27]	1	2	1	3	1	1	1	3	2	**2**	**Fair**

Skouroliakou et al. 2005[28]	2	2	2	4	4	4	2	3	3	**3**	**Poor**
Tavakoli-Ardakani et al. 2013[29]*	2	3	2	3	2	3	0	3	2	**2**	**Fair**
Terkola et al. 2017[30]	1	1	2	3	4	2	2	3	2	**2**	**Fair**
van den Heever et al. 2016[31]	1	1	1	2	2	3	1	2	1	**2**	**Fair**
Westbrook et al. 2011[32]	2	1	3	3	2	2	2	3	1	**2**	**Fair**
Wheeler et al. 2008[33]	1	3	2	3	1	4	2	3	1	**2**	**Fair**
Yin et al. 2016[34]	2	1	1	2	2	2	1	2	2	**2**	**Fair**

Studies are rated as good (1), fair (2), poor (3), or very poor (4) for each of the Hawker criteria, and given an overall score based on the average rating across all criteria.

*This study could not be fully evaluated due to a missing table in the available publication.

Table S3. Study Characteristics

Study	Geographical Location(s)	Centers, n	Patient Population	Study Design	Observational Technique	Type of Intravenous Admixture	Location of Intravenous Admixture Preparation	Method of Intravenous Admixture Preparation	Patient Impact Measured (Yes / No)
Anselmi et al. 2007[1]	Brazil	3	General inpatient units	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	No
Aruna et al. 2015[2]	India	1	General inpatient units	Single arm	Chart review	Multiple IV therapies	Not specified	Manual	No
Bertsche et al. 2008[3]	Germany	1	General inpatient units and ICU	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes
Campino et al. 2016[4]	Spain	11	NICU	Comparative	Final concentration of admixture	Multiple IV therapies	Central pharmacy vs nursing ward	Manual	No
Castagne et al. 2011[5]	France	1	Oncology inpatients	Single arm	Final concentration of admixture	Chemotherapy	Central pharmacy	Automated	No
Cousins et al. 2005[6]	France Germany UK	3	General medical and surgical inpatients	Single arm	Direct observation (participants in France and Germany were blinded to study purpose)	Multiple IV therapies	Nursing ward	Manual	No
Crill et al. 2010[7]	US	1	Critical care (NICU)	Single arm	Bacterial culture	Intravenous fat emulsion	Central pharmacy	Manual	Yes
Dehmel et al. 2011[8]	Germany	1	Critical care (ICU)	Comparative	Final concentration of admixture	Multiple IV therapies	Central pharmacy vs nursing ward	Automated vs manual	No
Ding et al. 2015[9]	China	1	General surgery inpatients	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes
Fahimi et al. 2007[10]	Iran	1	Critical care (ICU)	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes
Fahimi et al. 2008[11]	Iran	1	Critical care (ICU)	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes

Helder et al. 2016[12]	Netherlands	1	NICU, PICU, and general pediatric wards	Interventional	Direct observation	Multiple IV therapies	Nursing ward	Manual	No
Hoefel et al. 2006[13]	Brazil	1	General units and ICU	Single arm	Direct observation	Antibiotic (cefepime)	Nursing ward	Manual	No
Khalili et al. 2013[14]	Iran	3	Adult and pediatric inpatients	Comparative	Bacterial culture	Multiple IV therapies	Central pharmacy vs nursing ward	Manual	No
Macias et al. 2005[15]	Mexico	1	Critical care (NICU)	Single arm	Bacterial culture	Multiple IV therapies	Nursing ward	Manual	No
MacKay et al. 2009[16]	US	1	Pediatric trauma unit	Interventional	Cross-check	Multiple IV therapies	Central pharmacy	Automated	No
Masini et al. 2014[17]	Italy	1	Inpatient and outpatient oncology	Comparative	Final concentration of admixture	Chemotherapy	Central pharmacy	Automated vs manual	No
Moniz et al. 2014[18]	US	1	Pediatric inpatients	Single arm	Direct observation; Pharmacists reviewed digital photos of each preparation step via a web application	Multiple IV therapies	Central pharmacy	Automated	Yes
Nguyen et al. 2014[19]	Vietnam	1	Critical care (ICU / PSU)	Interventional	Direct observation (participants were blinded to study purpose)	Multiple IV therapies	Not specified	Manual	Yes
Niemann et al. 2015[20]	Germany	1	Pediatric inpatients	Interventional	Direct observation	Multiple IV therapies	Not specified	Manual	Yes
Ong et al. 2013[21]	Malaysia	1	General and acute care, adult and pediatric inpatients	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	No
Parshuram et al. 2006[22]	Canada	1	Pediatric oncology (not specified if inpatient or outpatient)	Single arm	Final concentration of admixture	Chemotherapy	Not specified	Not specified	No
Rashed et al. 2016[23]	UK	1	Pediatric inpatients	Comparative	Direct observation and final concentration of infusion	Morphine	Nursing ward vs operating theater	Manual	No

Reece et al. 2016[24]	US	1	Oncology outpatients	Comparative	Error reports (self-reported and automated)	Chemotherapy	Central pharmacy	Manual	No
Rodriguez-Gonzalez et al. 2012[25]	Spain	1	Gastroenterology inpatients	Single arm	Direct observation (participants were blinded to study purpose)	Multiple IV therapies	Not specified	Not specified	Yes
Sacks et al. 2009[26]	US	1	General adult and pediatric inpatient units and ICU	Single arm	Incident reports	Total parenteral nutrition	Central pharmacy	Automated	Yes
Seger et al. 2012[27]	US	1	Oncology inpatients	Comparative	Direct observation	Chemotherapy	Central pharmacy	Automated vs manual	Yes
Skouroliakou et al. 2005[28]	Greece	1	Neonatal inpatients	Comparative	Cross-check and direct observation	Total parenteral nutrition	Not specified	Automated vs manual	No
Tavakoli-Ardakani et al. 2013[29]	Iran	1	Hematology and oncology inpatients and outpatients	Single arm	Direct observation	Chemotherapy	Nursing ward	Manual	No
Terkola et al. 2017[30]	Austria Czech Republic Denmark Germany Switzerland	10	Oncology	Single arm	Incident reports	Chemotherapy	Offsite pharmacy	Not specified	No
van den Heever et al. 2016[31]	South Africa	1	Obstetric surgery	Single arm	Bacterial culture	Phenylephrine	Obstetric theater	Manual	No
Westbrook et al. 2011[32]	Australia	2	General and surgical inpatients	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes
Wheeler et al. 2008[33]	UK	1	Critical care (neurological) inpatients	Interventional	Cross-check	Multiple IV therapies	Nursing ward	Manual	No
Yin et al. 2016[34]	Malaysia	1	Critical care (ICU)	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	No

Method of preparation was assumed to be manual for studies in which IV admixture preparation occurred in the nursing ward, and no other information regarding method of preparation was provided.
ICU, intensive care unit; IV, intravenous; NICU, neonatal intensive care unit; PSU, post-surgical unit; UK, United Kingdom; US, United States.

Table S4. Patient Burden of Harm

Study	Error Types	Burden of Harm
NCC MERP Medication Error Index Definition of Error Severity		
Fahimi et al. 2007[10]	Wrong drug Wrong label Wrong dose	All observed errors were rated NCC MERP Index Category B ("An error occurred but the error did not reach the patient.")
Rodriguez-Gonzalez et al. 2012[25]	Wrong diluent solution Wrong diluent volume	• Severity was defined according to updated medication errors taxonomy adapted from NCC MERP definitions.[35] • Severity of wrong preparation errors (reconstitution and dilution) were determined to have the potential to cause "no damage."
Sacks et al. 2009[26]	Composite	Severity of errors was defined according to the NCC MERP Index: • 91% of errors did not cause harm (Categories B–D) • 15% of errors were "near misses" (Categories A–B) • 8% of errors contributed to or resulted in temporary harm (Categories E–F) No errors resulted in permanent harm, near death, or death (Categories G–I)
Clinician Assessment or Expert Panel Definition of Error Severity		
Bertsche et al. 2008[3]	Inadequate aseptic technique	• A multidisciplinary committee for quality assurance established risk scores for medical errors. • Errors were assigned a risk score weighted by potential risk of the drug involved and the characteristics of the error (low risk = 0.5, moderate risk = 1, high risk = 2). • Rates of error by severity were reported for all types of administration combined (IV, oral, and gastric tube), but not separately.
Moniz et al. 2014[18]	Wrong dose Wrong drug Wrong diluent solution Inadequate aseptic technique Composite	A new workflow was implemented that detected IV preparation errors that would not have been detected previously. These new errors (n = 447) were rated: • Little potential for harm: 62.64% • Potential ADE with moderate harm: 32.66% • Potential ADE with severe harm: 4.70%
Nguyen et al. 2014[19]	Wrong drug	Clinical relevance of each dose with ≥ 1 error was rated on a validated scale ranging from 0 (no harm) to 10 (death) by a panel of healthcare providers, and was categorized as follows: • Minor outcome: 0–2

Table S4. Patient Burden of Harm

Study	Error Types	Burden of Harm
	Wrong dose	• Moderate outcome: 3–7 • Severe outcome: 8–10 Moderate and severe outcomes were considered clinically relevant (57.9% to 64.0% of errors across the 2 study wards).
	Composite	
Niemann et al. 2014[20]	Wrong diluent solution	Clinical relevance of error subcategories was rated by an expert panel on a four-point scale: 1. No clinical relevance 2. Minor clinical relevance
	Wrong diluent volume	3. Clinical relevance 4. High clinical relevance The frequency of each level of severity combined oral and IV drug errors.
	Composite	
Seger et al. 2012[27]	Wrong drug	• Severity was rated as life-threatening, severe, significant, or little-to-no harm. • Events with potential for little-to-no harm were not included in the analysis. • There were no potentially life-threatening events, and the remaining events were approximately evenly distributed between significant and serious.
	Wrong concentration	Doses with ±5% to 10% variance were considered to have little to no potential for harm. Those with variance > ±10% were rated serious and potentially harmful.
Westbrook et al. 2011[32]	Wrong drug	• Severity was rated on a scale from 1 ("Incident is likely to have little to no effect on the patient") to 5 ("Incident is likely to lead to death"), with ratings of 1 to 2 considered minor errors and 3 to 5 considered serious errors. • 25.5% of overall errors were rated as serious.
	Wrong diluent solution	• 23.8% of wrong diluent solution errors were rated as serious.
	Wrong diluent volume	• 17.4% of wrong diluent volume errors were rated as serious.
Other Method for Determination of Error Severity		
Crill et al. 2010[7]	Inadequate aseptic technique Bacterial contamination	• Severity of errors was not rated. • Authors noted that no cases of systemic infection arose from syringes that had positive cultures.
Ding et al. 2015[9]	Wrong dose	• An error was considered clinically important if it concerned a drug listed in the ISMP list of high-alert medications (2008). • 81% of TPN dose errors involved ISMP high-alert medications.

Table S4. Patient Burden of Harm

Study	Error Types	Burden of Harm
Fahimi et al. 2008[11]	Composite Wrong diluent solution Wrong dose	An error was considered clinically important if it concerned a drug listed in the ISMP list of high-alert medications (2008). There was no severity rating system, but the authors note that none of the errors identified resulted in adverse effects or major risks to patients.

ADE, adverse drug event; ISMP, Institute for Safe Medication Practices; IV, intravenous; NCC MERP, National Coordinating Council for Medication Error Reporting and Prevention; TPN, total parenteral nutrition.

Table S5. Error Incidence Definitions

Admixture Preparation and Labeling Error Types	Definitions	Study
Component Error		
Wrong Drug	An IV drug was prepared or administered that differed from the one that was prescribed	Anselmi et al. 2007[1] Cousins et al. 2005[6] Moniz et al. 2014[18] Nguyen et al. 2014[19] Ong et al. 2013[21] Reece et al. 2016[24] Seger et al. 2012[27] Westbrook et al. 2011[32]
	An unauthorized IV drug was administered, or an order was changed, that was not found in the patient chart	Fahimi et al. 2007[10]
	An incorrect drug or dosage form was selected	Yin et al. 2016[34]
Wrong Diluent Solution	An IV drug was prepared or administered with a diluent that was not compatible with drug and volume to achieve the correct concentration	Cousins et al. 2005[6]
	An IV drug was prepared with the incorrect diluent based on any of the following: • The manufacturer's instructions • Published drug preparation handbooks • Other internal or external drug preparation guidelines	Fahimi et al. 2008[11] Niemann et al. 2015[20] Ong et al. 2013[21] Westbrook et al. 2011[32]
	An IV drug was prepared with the incorrect diluent	Moniz et al. 2014[18] Rashed et al. 2016[23] Reece et al. 2016[24]
	The IV medication was reconstituted or diluted incorrectly according to medication errors taxonomy adapted from NCC MERP definitions [Otero Lopez 2008]	Rodriguez-Gonzalez et al. 2012[25]
Wrong label	An IV drug was prepared or administered with a missing or incomplete label with respect to drug name, dose, patient name, or preparation time	Cousins et al. 2005[6]
	The administration rate, patient identification, date, or time of infusion was not properly documented	Fahimi et al. 2007[10]
	The IV drug label was incomplete with respect to patient, drug, dose, or preparation time, or the opened diluent vials were improperly labeled	Ong et al. 2013[21]

	Syringes or drug infusion containers were not labeled properly	Yin et al. 2016[34]
	Label was incomplete or incorrect with regard to name of solution, concentration of solution, date of preparation, time or preparation, or healthcare worker's signature	van den Heever et al. 2016[31]
	The syringe label was illegible or missing the drug name, dose, concentration, diluent, patient name, patient location, preparer's initials, countersigned, date, or time	Wheeler et al. 2008[33]
Dose or Calculation Error		
Wrong Dose	An incorrect IV drug dose or infusion volume was prepared or administered	Anselmi et al. 2007[1] Cousins et al. 2005[6] Fahimi et al. 2007[10] Hoefel et al. 2006[13] Moniz et al. 2014[18] Reece et al. 2016[24]
	The calculated concentration deviated by >10% of that prescribed	Campino et al. 2016[4]
	An ingredient deviated > ±10% from the correct volume or concentration, a dose was omitted, or an extra dose was given	Ding et al. 2015[9]
	An IV drug that differed by ±10% of the prescribed dose was prepared	Nguyen et al. 2014[19]
	An incorrect dose or diluent volume was calculated that differed from the manufacturer's instructions or published drug preparation handbooks	Fahimi et al. 2008[11]
Wrong Concentration	The sampled IV drug preparation deviated by ±20% or more from its intended concentration	Castagne et al. 2011[5]
	The sampled IV drug preparation deviated by ≥ ±5% or ≥ ±10% from its intended concentration	Dehmel et al. 2011[8] Masini et al. 2014[17]
	The sampled IV drug preparation deviated by ±10% or more from its intended concentration	Parshuram et al. 2006[22]
	The sampled IV drug preparation deviated by more than ±10% from its intended concentration	Campino et al. 2016[4] Yin et al. 2016[34]
	The morphine infusion deviated from its target concentration beyond the pharmacopoeial limit for drug content of morphine sulphate injection (92.5–107.5%)	Rashed et al. 2016[23]
	The sampled IV drug preparation deviated by ±5% or more from its intended concentration	Seger et al. 2012[27]
	The concentration of any of the individual components of total parenteral nutrition was calculated incorrectly	Skouroliakou et al. 2005[28]
	The volume of the sampled IV drug preparation exceeded the gravimetric software's preset tolerance limit • Tolerance levels were set by each site and ranged from 2.5–6%	Terkola et al. 2017[30]

Wrong Diluent Volume	An incorrect diluent volume was used	Cousins et al. 2005[6] Hoefel et al. 2006[13] Reece et al. 2016[24]
	An IV drug was prepared with an incorrect diluent volume based on any of the following: • The manufacturer's instructions • The corresponding summaries of product characteristics • Published drug preparation handbooks • Other internal or external drug preparation guidelines	Niemann et al. 2015[20] Ong et al. 2013[21] Westbrook et al. 2011[32]
	The IV medication was reconstituted or diluted incorrectly according to medication errors taxonomy adapted from NCC MERP definitions [Otero Lopez 2008]	Rodriguez-Gonzalez et al. 2012[25]
	The total volume of the IV solution was incorrect	Skouroliakou et al. 2005[28]
Aseptic Technique Error		
Inadequate Aseptic Technique	The IV drug was not prepared in accordance with local hygiene guidelines	Bertsche et al. 2008[3]
	Sampling of repackaged syringes resulted in positive bacterial cultures	Crill et al. 2010[7]
	Nonadherence to 1 or more of the following hygiene protocols: • Hand disinfection by applying hand alcohol • Rubbing hands for 30 seconds • Using sterile gloves • Disinfecting the ampoule • Allowing the ampoule to dry for 30 seconds	Helder et al. 2016[12]
	Aseptic technique was not followed during IV infusion preparation	Rashed et al. 2016[23] Yin et al. 2016[34]
	Needles or syringes were left uncapped during IV preparation	Moniz et al. 2014[18]
Bacterial Contamination	Sampling of IV drug preparations resulted in positive bacterial cultures	Crill et al. 2010[7] Khalili et al. 2013[14] Macias et al. 2005[15] van den Heever et al. 2016[31]
Failure to Disinfect Vial	Vial top or ampoule was not disinfected during preparation	Cousins et al. 2005[6] Helder et al. 2016[12] Ong et al. 2013[21] Rashed et al. 2016[23]

Improper Hand Hygiene	Hands were not washed, gloves were not worn, or nonsterile gloves were worn during IV drug preparation	Cousins et al. 2005[6] Ong et al. 2013[21]
	Gloves were not worn during IV infusion preparation	Rashed et al. 2016[23]
Composite Error		
Any Admixture or Labeling Error	An IV drug dose was prepared or administered differently from how it was prescribed by the physician in the patient's medical record with regard to: • Wrong patient • Wrong drug • Wrong dose • Omitted dose	Anselmi et al. 2007[1]
	An IV drug was incorrectly formulated or manipulated before administration: • Incorrect reconstitution or dilution • Physicochemical incompatibility of drugs mixed in the same container • Wrong pharmaceutical form	Aruna et al. 2015[2]
	Any of the following IV preparation or administration errors occurred: • Unordered drug • Omitted drug • Wrong dose • Extra dose • Wrong route of administration	Ding et al. 2015[9]
	A drip compounding error of greater than 1 standard deviation from the calculated value for each component in parenteral nutrition preparations occurred	MacKay et al. 2009[16]
	IV drug preparations in the institution were prepared and verified using an IV workflow manager system. Doses that were reworked or rejected were retrospectively reviewed for errors in: • Preparation • Aseptic technique • Documentation	Moniz et al. 2014[18]
	Any IV of the following IV preparation or administration errors occurred: • Wrong drug • Wrong dose • Wrong dosage form • Deteriorated drug • Wrong preparation technique • Omission • Unordered drug • Wrong administration technique	Nguyen et al. 2014[19]
	At least 1 deviation from internal or external drug preparation or administration guidelines, corresponding summaries of product characteristics, or manufacturer recommendations occurred during the drug handling processes (eg, preparation, storage, labeling)	Niemann et al. 2015[20]

	Documented events in parenteral nutrition preparation or administration: • Dose omission • Extra dose • Prescription or refill delayed • Drug list incorrect • Monitoring error • Unauthorized drug • Inadequate pain management • Wrong events (eg, dose, drug, time, patient)	Sacks et al. 2009[26]
	A drug was prepared using the incorrect diluent or incorrect volume, or was not mixed properly	Yin et al. 2016[34]
	A deviation in handling, preparation, or administration of an IV drug occurred based on: • The manufacturer's instructions • *Handbook on Injectable Drugs*, 15th ed. • *Drug Information Handbook*, 19th ed. • American Society of Health-System Pharmacists Drug Information • *Oncology Nursing Drug Handbook*	Tavakoli-Ardakani et al. 2013[29]
IV, intravenous; NCC MERP, National Coordinating Council for Medication Error Reporting and Prevention		

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	10
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	41-43
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	13-16
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	26
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	30
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	30
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	31

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Systematic evidence review of rates and burden of harm of intravenous admixture drug preparation errors in healthcare settings

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Systematic evidence review of rates and burden of harm of intravenous admixture drug preparation errors in healthcare settings

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ABSTRACT (300/300)

Objective: To examine published evidence on intravenous (IV) admixture preparation errors (IAPEs) in healthcare settings.

Methods: Searches were conducted in 3 electronic databases (January 2005 to April 2017). Publications reporting rates of IAPEs and error types were reviewed and categorized into the following groups: component errors, dose/calculation errors, aseptic technique errors, and composite errors. The methodological rigor of each study was assessed using the Hawker method.

Results: Of the 34 articles that met inclusion criteria, 28 reported the site of IAPEs: central pharmacies (n = 8), nursing wards (n = 14), both settings (n = 4), and other sites (n = 3). Using the Hawker criteria, 14% of the articles were of good quality, 74% were of fair quality, and 12% were of poor quality. Error types and reported rates varied substantially, including wrong drug (~0% to 4.7%), wrong diluent solution (0% to 49.0%), wrong label (0% to 99.0%), wrong dose (0% to 32.6%), wrong concentration (0.3% to 88.6%), wrong diluent volume (0.06% to 49.0%), and inadequate aseptic technique (0% to 92.7%). Four studies directly compared incidence by preparation site and/or method, finding error incidence to be lower for doses prepared within a central pharmacy versus the nursing ward, and lower for automated preparation versus manual preparation. Although 8 studies (24%) reported ≥1 errors with the potential to cause patient harm, no study directly linked IAPE occurrences to specific adverse patient outcomes.

Conclusions: The available data suggest a need to continue to optimize the IV preparation process, focus on improving preparation workflow, design and implement preventive strategies, train staff on optimal admixture protocols, and implement standardization. Future research should focus on the development of consistent error subtype definitions, standardized reporting

methodology, and reliable, reproducible methods to track and link risk factors with the burden of harm associated with these errors.

Strengths and limitations of this study

- To the authors' knowledge, this is the first systematic review conducted that attempts to categorize intravenous admixture preparation errors (IAPEs) according to both the characteristics of the error and the location and method of intravenous (IV) preparation.
- Although IAPE is a safety concern, its frequency, subtypes, and associated burden of harm are not well understood; thus, the current review presented a thoughtful and valid framework to assess IAPEs within their procedural context.
- This review attempted to include all articles published in English between January 2005 and April 2017 that reported on IAPEs in which healthcare professionals prepared ≥1 dose of IV administered therapy.
- This review is limited by the number of studies identified that reported data on the frequency and/or burden of harm of IAPEs.

INTRODUCTION

Errors in medication preparation and administration can lead to patient harm.[1-3] For example, many preventable adverse events with respect to medication have been linked to errors in dosing (eg, patients receiving higher or lower amounts of medication than intended).[2, 4] The medication use cycle for an intravenous (IV) medication involves multiple steps prior to administration, including prescribing and transcription (paper-based orders), in addition to a number of admixture preparation and labeling steps (**Figure 1**).

Figure 1. Intravenous medication use cycle

An IV admixture preparation error (IAPE) can be considered as any deviation from the specifications involved in the admixture preparation and labeling process. An IAPE is a form of medication error—in other words, a preventable adverse event resulting from inappropriate medication preparation, administration, or use that can lead to patient harm, including death, while the medication is in the control of the healthcare professional, patient, or consumer.[5, 6]

IAPEs can be introduced at multiple points during admixture preparation and labeling. These steps can occur on site at a nursing ward or in a central or satellite pharmacy. IV medication doses are typically prepared (1) manually by nurses, either at the bedside or in a ward-based preparation room, (2) manually by pharmacists and pharmacy technicians in a central or satellite clean room under a laminar-airflow hood, or (3) through the use of pharmacy automation technology, which can be partially or fully automated and may be located in clean rooms or clean compartments within the machine. United States data suggest increasing use of automated technologies aimed at reducing IAPEs, for technologies ranging from robotic chemotherapy compounding devices (0.3% of hospitals) to barcode verification (20% of

hospitals), with higher levels of adoption predominantly within larger hospitals.[7] Delivery of the correct dose of an IV admixture to a patient depends on the careful control of many factors, such as the calculation of a patient-specific dose (eg, based on body weight or organ function), oversight of procedures utilized for admixture preparation, and labeling practices.[4, 8] While research suggests that the highest medication-error rates can be attributed to the prescribing and administration phases of the medication use cycle,[9-11] studies focused on medication preparation practices suggest that the IV admixture preparation and labeling phase pose a significant potential for errors.[9, 12-15] It is unknown what proportion of IAPEs are unreported.

In addition to measuring the incidence of IAPEs, it is also important to understand their impact in terms of burden of harm. Two examples of existing frameworks for categorizing patient harm resulting from medication errors are The Institute for Safe Medication Practices (ISMP) high-alert medication lists and The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Medication Error Index. ISMP publishes information and educational resources for healthcare providers on preventing medication errors, and tracks voluntary medication errors reports. Based on these voluntary error reports, ISMP maintains lists of high-alert medications in outpatient and inpatient settings that have the potential for increased risk of patient harm if used in error.[16] The NCC MERP Medication Error Index groups medication errors into nine possible categories, ranging from non-errors (situations in which errors may occur) to errors resulting in patient death.[17] These categories also include near-miss (near-hit) situations in which an error occurred but did not reach the patient or cause harm. ISMP uses the NCC MERP Medication Error Index in its medication error database.

Much of the prior published research focusing on the prescription or administration of IV therapies has failed to describe or distinguish between errors that arise as a result of the

admixture preparation process versus errors associated with incorrect prescribing or administration.[18-21] With this systematic review, our objective is to identify the incidence of IAPEs (overall and by subtype) reported across institutional healthcare settings and to understand the frequency of error subtypes and associated burden of patient harm attributable to IAPEs as reported in the published literature.

METHODS

Identification of literature and data sources

For the purposes of this review, an IAPE was defined as an error or deviation at any step within the admixture preparation process where the drug container was physically handled or manipulated by a healthcare professional. A broad search strategy was developed to identify all studies (published from January 2005 to September 2015) that mention any type of IAPE in an institutional healthcare setting, which included reports relating to wrong drug, wrong diluent solution, wrong label, wrong dose, wrong concentration, wrong diluent volume, and inadequate aseptic technique. Dose omission errors were considered to be errors related to administration rather than preparation and, thus, were not included as a focus in this study. Near-miss and actual errors (those that did reach patients) were both included. The review was structured based on the PICOS (patients, intervention, comparator, outcomes, and study design) search strategy (**Table 1**).

Table 1. PICOS Search Strategy

Patient/Problem	Incorrect preparation of IV admixtures within an institutional healthcare setting (acute or long-term care) by a licensed healthcare professional (nursing and/or pharmacy staff and/or physician) team member

Intervention	Preparation of an IV admixture
Comparison	Automated versus manual preparation methods (studies were not required to demonstrate both) Central pharmacy versus on-unit (on the nursing ward) preparation location (studies were not required to demonstrate both)
Outcome	Incorrectly prepared or labeled IV admixture, which may or may not have reached a patient: • Wrong drug or diluent • Wrong dose, concentration, or volume • Wrong, inaccurate, or omitted label • Contaminated admixture or failure to follow hygiene or sterility protocols • A combination of the above
Study Types	**Inclusion criteria:** Observational studies for which numerator (number of doses impacted or number of errors) and denominator (number of eligible doses or opportunities for error) are discernible **Exclusion criteria:** Studies in which isolated contamination volumes are reported but for which total batch size is unknown fail to qualify for consideration Error report logs for which number of errors is known but associated number of prepared doses is not also fail to qualify

IV, intravenous; PICOS, patients, intervention, comparator, outcomes, and study design..

Systematic review process

Three electronic databases were searched for relevant literature reporting on IAPE: Ovid MEDLINE, EMBASE, and International Pharmaceutical Abstracts. The initial search was conducted on February 6, 2014, with supplementation on September 4, 2015 to include articles published during the interim. Aggregate results include articles published in English between January 2005 and April 2017 that involved studies in human subjects in which a healthcare professional prepared ≥1 doses of IV administered therapy (medication, including total parenteral nutrition). This date range was selected to include a sufficiently long period to capture the studies of interest, while remaining relevant to current practice in terms of technology and guidelines. Key search terms and limits used in the systematic review are shown in **online supplementary Table S1**. Screenings for relevant literature citations that appeared in the publications were made during the review process to identify any pertinent, additional publications up to April 2017. For this systematic review, references had to meet the

inclusion/exclusion criteria detailed in the next section. Duplicate articles were removed electronically prior to manual review. Titles of the papers and abstracts captured in the electronic search results were screened by 2 reviewers for relevancy according to prespecified criteria. If the titles did not provide sufficient information for screening, the abstract or full-text articles were then reviewed to discern whether the publication met inclusion criteria. All publications that met entry criteria for the review were obtained as full-text articles and then reassessed by the reviewers against the review criteria. The review process was fully compliant with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22]

Inclusion and exclusion criteria

Publications reporting on a randomized, controlled trial, prospective cohort study, observational quality audit, descriptive study, quasi-experimental study, or quality-improvement study were selected for inclusion. Quasi-experimental studies, quality-improvement studies, and descriptive studies were eligible if they included sufficient data on the number of doses prepared. While systematic reviews reporting on these study types were not included, their respective reference lists were reviewed to identify potentially relevant studies. Publications were not limited to a single geographic or physical study location and may have occurred in the hospital or any other institutional or outpatient healthcare setting associated with a hospital.

Publications and studies were included for review if they either reported incidence of IAPE or provided sufficient detail for incidence calculation. These errors included incorrectly dispensed medication as well as near-misses that were caught by the study observer prior to administration. Errors also had to originate with a healthcare professional (eg, nurse or pharmacist). Studies reporting patient or informal caregiver medication errors were not included.

To be included, studies were required to report original data on IAPEs, including a denominator, to allow for incidence calculations.

Articles that described only errors in prescribing, transcription, administration, and monitoring were not included. In addition to all articles that failed to meet the aforementioned inclusion criteria, the following article types were also excluded: conference abstracts, case reports, simulations, and survey findings.

Data extraction

The data extracted from relevant articles for analysis included year of publication, country of origin, study period, patient population, definition of error, IV preparation location (eg, central or satellite pharmacy or nursing ward), care setting (eg, critical care, general nursing ward), type of therapy, method of error detection, and error incidence. Data were extracted and scored independently by 2 separate reviewers, with introduction of a third reviewer in the case of scoring discrepancies, with all differences being resolved by consensus. Each review team included ≥1 pharmacist for professional knowledge and understanding of drug preparation. The methodological rigor of each study was critically appraised and scored using the Hawker method.[23] This appraisal tool is simple and particularly adaptable to literature reviews encompassing varied research methodologies.[24] It employs 9 criteria to evaluate for each study: 1) abstract and title; 2) introduction and aims; 3) method and data; 4) sampling; 5) data analysis; 6) ethics and bias; 7) results; 8) transferability or generalizability; and 9) implications and usefulness. For each criterion, studies were scored as: good (score 4), fair (score 3), poor (score 2), or very poor (score 1). A mean score was then calculated for each study across all 9 criteria, and the overall quality of each study was likewise scored from good to very poor.

For the purposes of this review, IAPEs were grouped into 1 of 4 categories based on the characteristics of the error and the location and method of IV preparation. Component errors were defined as all those that result from selecting an incorrect ingredient (ie, wrong drug or wrong diluent solution), or applying an incorrect, incomplete, or inaccurate label (ie, wrong label) to the admixture. Dose/calculation errors were defined as those involving the use of an incorrect calculation to determine dose and/or diluent amount, or the use of a diluent volume not in accordance with the package insert (ie, wrong dose, wrong concentration, and wrong diluent volume). Aseptic technique errors involved a breakdown in the process designed to minimize the potential for antimicrobial contamination (ie, inadequate aseptic technique, bacterial contamination, failure to disinfect vial, and improper hand hygiene). The category of composite errors was used to describe IAPE rates reported in aggregate, in which the researchers reported an overall rate that included multiple IAPE subtypes. Composite errors included cases in which >1 error or type of error was observed in a single preparation.

This study was registered with the PROSPERO international database of systematic reviews (CRD42014010418) to comply with PRISMA guidelines.

RESULTS

Electronic database searches yielded 2018 English language publications for review. Additional sources (hand searches of publication reference lists) identified another 3 publications for evaluation. After removing duplicates and screening for inclusion and exclusion criteria, 34 articles were included in the final synthesis (**Figure 2**).[3, 25-57] Of the 34 articles, 5 (15%) were rated good quality,[30, 34, 38, 45, 46] 25 (74%) were fair quality,[3, 25-29, 31-33, 36, 37, 39-41, 43, 44, 48, 51-57] and 4 (12%) were poor quality[35, 42, 49, 50] after assessment using the Hawker method. The quality of 1 study (3%) could not be fully scored due to a missing data

table in the available publication.[47] Details of the Hawker analysis for each study are shown in online **supplementary Table S2**.

Figure 2. PRISMA study inclusion flow diagram

Study characteristics

A summary of the study characteristics, in terms of the setting and methodology, described in the 34 publications is presented in **Table 2**. Collectively, the publications reported international data, with studies spanning Africa, North America, South America, Europe, the Eastern Mediterranean region, and the Western Pacific region. Patient populations varied across studies, with both adults and children represented. Studies were conducted mainly in general inpatient or critical care settings, with several in pediatric or hematology units. The majority of publications (21 [62%]) assessed errors in >1 type of IV therapy. Additional individual details for each study are shown in online **supplementary Table S3**.

Table 2. Summary of study characteristics

Study Setting Characteristics	n (%)	Study Methodology Characteristics	n (%)	IV Admixture Preparation Characteristics	n (%)
Geographical region		**Study design**		**Location of IV admixture preparation**	
Europe	13 (38)	Single arm	21 (62)	Nursing ward	13 (38)
Americas	10 (29)	Interventional	8 (24)	Central pharmacy	8 (24)
Western Pacific	6 (18)	Comparative	5 (15)	Not specified	6 (18)
Eastern Mediterranean	4 (12)			Nursing ward and central pharmacy	4 (12)
Africa	1 (3)	**Observational technique**		Nursing ward and operating theater	1 (3)
		Direct observation	17 (50)	Offsite pharmacy	1 (3)
Number of sites		Analysis of final concentration	5 (15)	Obstetric theater	1 (3)
Single-center	28 (82)	Bacterial culture	4 (12)		
2 centers	3 (9)	Cross-checking	3 (9)	**Method of IV admixture preparation**	
3 or more centers	3 (9)	Incident report	3 (9)	Manual	22 (68)
		Chart review	1 (3)	Automated	4 (12)
Patient population		Direct observation and analysis of final concentration	1 (3)	Manual vs automated	4 (12)
Not specified	15 (44)			Not specified	3 (9)
Pediatric patients	10 (29)				
Adult patients	6 (18)	**Measurement of patient impact**		**Types of IV therapies**	
Adult and pediatric patients	3 (9)	Not measured	22 (65)	Multiple	21 (62)
		Clinician assessment or expert panel	6 (18)	Chemotherapy	7 (21)
Care setting		NCC MERP medication error index	3 (9)	Parenteral nutrition or IV lipid emulsion	3 (9)
Critical care*	9 (26)	Other	2 (6)	Antibiotic	1 (3)
General inpatient wards	8 (24)	ISMP high-alert medication	1 (3)	Morphine	1 (3)
Pediatric units	7 (20)			Phenylephrine	1 (3)
Oncology and/or hematology†	6 (18)				
General inpatient and critical care	3 (9)				
Obstetrics	1 (3)				

*Includes intensive care, neonatal intensive care, post-surgical, and neurologic critical care
†Inpatient and/or outpatient
ISMP, Institute for Safe Medication Practices; IV, intravenous; NCC MERP, National Coordination Council for Medication Error Reporting.;

The most common method of detecting errors was direct observation, used in 17 studies (50%),[3, 25, 26, 28, 31-33, 37, 41, 44-48, 52, 55] and 1 study used direct observation and analysis of final IV admixture concentration.[53] Other methods included analysis of final concentration in 5 studies (15%),[27, 30, 36, 38, 51] bacterial culture in 4 studies (12%),[29, 34, 49, 57] cross-checking in three studies (9%),[35, 42, 43] incident reports in 3 studies (9%),[40, 54, 56] and chart review in one study.[50] In several studies using the direct observation method, nurses or pharmacists preparing the IV admixtures consented to participate but were not fully aware of the study aims to avoid influencing their behavior.[18, 39, 45] Eight studies (24%) reported on the accuracy of IV preparation before and after an intervention,[35, 36, 41-43, 45, 46, 52] 5 studies (15%) compared IV admixture preparation locations or methods,[30, 36, 41, 42, 49] and the remaining 21 publications (62%) were single-arm studies.[3, 25-29, 31-34, 37-40, 44, 47, 48, 50, 55-57]

A total of 28 studies reported the IV preparation site. Of those studies, 14 publications (38%) reported preparation on the nursing ward[3, 25, 26, 28, 31-34, 37, 43, 47, 48, 52, 55] and 8 (24%) reported use of central pharmacies.[26, 27, 29, 35, 36, 40, 41, 44, 54] Three studies (12%) compared rates of IAPEs in the nursing ward and a central pharmacy[30, 49, 51] and 1 compared IAPEs in the nursing ward and operating theater.[53] Lastly, 2 studies reported IV preparation at offsite pharmacies[56] and in the obstetric theater,[57] respectively.

While IAPEs were not consistently linked with individual patient outcomes in the studies surveyed, nearly half of the studies attempted to assess the potential for patient impact in some way. Twelve (35%) of the publications included in this review reported on the severity of harm or potential for harm arising from identified IAPEs (see **online supplementary Table S2**), [3, 26, 29, 31, 32, 39-41, 44-46, 48] 8 (67%) of which reported ≥1 errors to result in various degrees

of harm,[3, 26, 40, 41, 44-46, 48] and 4 (33%) having reported no errors to have resulted in adverse outcomes or to have presented a major patient risk.[29, 31, 32, 39]

Of the 12 studies that reported on burden of harm, 3 (25%) used the NCC MERP medication error index[17] to score identified errors;[31, 39, 40] while 6 studies (50%) relied on clinician assessment or an expert panel for determination of error severity.[3, 26, 41, 44-46] Among the 6 studies that used clinician assessment or an expert panel, 2 of the study teams (Niemann et al[46] and Nguyen et al[45]) assessed errors based on clinical relevance rather than assigning a score based on patient harm or potential for harm. The remaining 3 studies each took a different approach to estimating patient harm.[29, 32, 48] Ding and colleagues[48] were the only authors to record whether the error was associated with a drug found on the ISMP list of high-alert medications. Crill and colleagues[29] did not have a system for rating error severity but did note that no contamination errors resulted in patient infections. Lastly, the 2008 study by Fahimi and colleagues[32] did not describe a specific system for rating error severity, but noted that none of the errors identified resulted in adverse events or major risks to patients. Further detail on how each study assessed patient burden of harm is shown in **online supplementary Table S4.**

Categorization and incidence of IAPEs

Errors identified in the selected studies were grouped into 4 broad categories: component errors, dose/calculation errors, aseptic technique errors, and composite errors, as detailed in the Methods section. Errors of the same subtype were frequently defined slightly differently among studies; full descriptions of the error subtype definitions are shown in **online supplementary Table S5**. Incidence values for error subtypes are presented in **Table 3**.

Table 3. Summary of Reported IAPE Incidence by Error Subtype

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
Anselmi et al. 2007[25]	Numerator: errors (including near-misses) Denominator: Doses prepared	Site 1: 0/804 Site 2: 0/100 Site 3: 1/487			Site 1: 8/804 Site 2: 2/100 Site 3: 36/487							Across all sites: 118/1391
	Incidence:	**0.00%–0.20%**			**0.90%–7.40%**							**8.48%**
Aruna et al. 2015[50]	Numerator: errors Denominator: cases											19/225
	Incidence:											**8.40%**
Bertsche et al. 2008[26]	Numerator: events Denominator: drug-handling processes							218/315				
	Incidence:							**69.20%**				
Campino et al. 2016[51]	Numerator: Errors Denominator: Doses prepared				NICUs: 6/444 Central pharmacy: 0/60			NICUs: 243/444 Central pharmacy: 23/60				
	Incidence:				**0.00%–1.35%**			**38.33%–54.73%**				
Castagne et al. 2011[27]	Numerator: errors (102 near-misses; 544 errors) Denominator: doses prepared					646/7382						
	Incidence:					**8.80%**						
Cousins et al. 2005[28]	Numerator: errors (not including near-misses)	UK: 0/273 GER: 0/425 FR: 0/100	UK: 2/273 GER: 208/425 FR:	UK: 118/273 GER: 421/425	UK: 1/273 GER: 7/425 FR: 5/100		13 /798 total			UK: 295/299 GER: 245/425	UK: 299/299 GER: 403/425	

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
	Denominator: doses prepared		18/100	FR: 20/100						FR: 4/100	FR: 9/100	
	Incidence:	**0.00%–0.00%**	**1.00%–49.00%**	**20.00%–99.00%**	**1.00%–5.00%**		**2.00%**			**4.00%–99.00%**	**9.00%–100%**	
Crill et al. 2010[29]*	Numerator: positive bacterial cultures Denominator: syringes prepared							3/90	3/90			
	Incidence:							**3.30%**	**3.30%**			
Dehmel et al. 2011[30]†	Numerator: errors Denominator: doses prepared					±5% deviation: 16/100 ±10% Deviation: 5/100						
	Incidence:					**5.00%–16.00%**						
Dehmel et al. 2011[30]‡	Numerator: errors Denominator: doses prepared					±5% deviation: 53/100 ±10% deviation: 22/100						
	Incidence:					**22.00%–53.00%**						
Ding et al. 2015[48]§	Numerator: errors Denominator: TOE (ordered and unordered doses)				50/593							54/593
	Incidence:				**8.43%**							**9.10%**
Fahimi et al. 2007[31]	Numerator: errors (including near-misses) Denominator: doses administered	2/43		4/43	14/43							
	Incidence:	**4.65%**		**9.30%**	**32.60%**							
Fahimi et al. 2008[32]¶	Numerator: errors (including near-misses) Denominator: doses prepared		49/524		38/524							

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
Helder et al. 2016[52]	**Incidence:**		**9.35%**		**7.25%**							
	Numerator: Errors Denominator: Doses prepared							177/191		98/191		
	Incidence:							**92.67%**		**51.31%**		
Hoefel et al. 2006[33]	Numerator: errors Denominator: doses administered				14/99		6/99					
	Incidence:				**14.10%**		**6.10%**					
Khalili et al. 2013[49]	Numerator: positive bacterial cultures Denominator: doses prepared								Nursing ward: 1/92 Central pharmacy: 0/17			
	Incidence:								**0.00–1.10%**			
Macias et al. 2005[34][‖]	Numerator: positive bacterial cultures Denominator: doses prepared								1/51			
	Incidence:								**1.45%**			
MacKay et al. 2009[35]**	Numerator: errors Denominator: 1000 doses prepared											0.66/1000
	Incidence:											**0.07%**
Masini et al. 2014[36][††]	Numerator: errors Denominator: doses prepared					5% relative error: 1/333 10% relative error: 4/333						
	Incidence:					**0.30%–1.20%**						
Moniz et al. 2014[44][‡‡]	Numerator: errors Denominator: doses prepared	8/ 425,683	3/ 425,683		857/ 425,683			11/ 425,683				2883/ 425,683

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
Nguyen et al. 2014[45][§§]	**Incidence:**	**~0.00%**	**~0.00%**		**0.20%**			**~0.00%**				**0.68%**
	Numerator: errors (including near-misses) Denominator: TOE (administered and omitted doses)	ICU: 1/236 PSU: 1/280			ICU: 27/236 PSU: 17/280							ICU: 159/236 PSU: 204/280
	Incidence:	**0.36%–0.42%**			**6.10%–11.40%**							**67.3%–72.90%**
Niemann et al. 2015[46]	Numerator: errors Denominator: drug-handling processes		38/233				115/233					138/233
	Incidence:		**16.00%**				**49.00%**					**59.00%**
Ong et al. 2013[37]	Numerator: errors (including near-misses) Denominator: doses administered	1/349	1/349	11/349			61/349			307/349	81/349	
	Incidence:	**0.28%**	**0.28%**	**3.20%**			**17.50%**			**88.00%**	**23.20%**	
Parshuram et al. 2006[38]	Numerator: errors Denominator: infusion bags prepared					24/78						
	Incidence:					**31.00%**						
Rashed et al. 2016[53]	Numerator: Errors (including near misses) Denominator: Doses prepared		Theater: 0/98 Nursing ward: 1/55			Theater: 31/35 Nursing ward: 17/43		Theater: 25/98 Nursing ward: 1/55		Theater: 98/98 Nursing ward: 55/55	Theater: 82/98 Nursing ward: 0/98	
	Incidence:		**0.00%–1.81%**			**39.53%–88.57%**		**1.81%–15.31%**		**100%–100%**	**0.00%–83.67%**	
Reece et al. 2016[54]	Numerator: Errors Denominator: Doses prepared:	Self-reported: 1/15,843 Software reported: 52/51,037	Self-reported: 4/15,843 Software reported: 5/51,037		Self-reported: 7/15,843 Software reported: 797/		Self-reported: 4/15,843 Software reported: 37/					

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
					51,037		51,037					
	Incidence:	**~0.00–0.01%**	**0.01%–0.03%**		**0.04%–1.56%**		**0.03%–0.07%**					
Rodriguez-Gonzalez et al. 2012[39]¶¶	Numerator: errors (including near-misses) Denominator: TOE (observed administrations plus omitted doses)		8/402				32/402					
	Incidence:		**1.99%**				**7.96%**					
Sacks et al. 2009[40]	Numerator: errors Denominator: doses prescribed											18/4730
	Incidence											**0.38%**
Seger et al. 2012[41]‖	Numerator: errors Denominator: doses prepared	3/1421				23/184						
	Incidence:	**0.21%**				**12.50%**						
Skouroliakou et al. 2005[42]	Numerator: errors Denominator: solutions prepared					20/941	8/941					
	Incidence:					**2.13%**	**0.85%**					
Tavakoli-Ardakani et al. 2013[47]†††	Numerator: errors Denominator: TOE											2705/8322
	Incidence:											**32.50%**
Terkola et al. 2017[56]	Numerator: Errors Denominator: Preparations					59,890/759,060						
	Incidence:					**7.89%**						

Reference	Error incidence calculation	Component Errors			Dose / Calculation Errors			Aseptic Technique Errors				Composite Errors
		Wrong Drug	Wrong Diluent Solution	Wrong Label	Wrong Dose	Wrong Concentration	Wrong Diluent Volume	General Inadequate Aseptic Technique	Bacterial Contamination	Failure to Disinfect Vial	Improper Hand Hygiene	Any Admixture or Labeling Error
van den Heever et al. 2016[57]	Numerator: Errors Denominator: Sampled preparations			0–101/110					7/110			
	Incidence:			**0.00–91.81%**					**6.36%**			
Westbrook et al. 2011[3]	Numerator: errors (including near-misses) Denominator: doses administered	1/568	21/568				121/568					
	Incidence:	**0.18%**	**3.70%**				**21.30%**					
Wheeler et al. 2008[43]	Numerator: errors Denominator: syringes prepared			88/149								
	Incidence:			**59.10%**								
Yin et al. 2016[55]* **	Numerator: Doses with ≥1 errors Denominator: TOE (observed administrations plus omitted doses)	0/122		15/122	1/122		14/122					69/122
	Incidence:	**0.00%**		**12.30%**	**0.82%**		**11.50%**					**56.66%**

* Crill et al. 2010[29]. Authors speculate that contamination arose during preparation, but note that it may also have occurred during or after administration.
† Dehmel et al. 2011[30]. Results presented for automated preparation in the centralized pharmacy.
‡ Dehmel et al. 2011[30]. Results presented for manual preparation in the nursing ward.
§ Ding et al. 2015[48]. Wrong dose error rate combines wrong dose, omission, and extra dose.
¶ Fahimi et al. 2008[32]. Wrong dose and wrong diluent volume were combined into 1 value in the original article.
‖ Macias et al. 2005[34]. This study was designed to observe a sepsis outbreak. Only baseline (pre-outbreak) data are presented in this table.
** MacKay et al. 2009[35]. This study tested automation as an intervention. Only baseline data is presented in this table.
†† Masini et al. 2014[36]. Results presented for manual preparation only.
‡‡Moniz et al. 2014[44]. Wrong volume of drug/diluent (detectable by previous practices), wrong drug volume (not detectable by previous practices), and wrong diluent volume (not detectable by previous practices) are combined in this table as wrong dose.
§§ Nguyen et al. 2014[45]. This was an interventional study. Only baseline data is presented in this table.
¶¶ Rodriguez-Gonzalez et al. 2012[39]. Errors were defined as "wrong reconstitution (volume, fluid)," which is reported in this table as wrong diluent solution, and "wrong dilution (volume, fluid)," which is reported in this table as wrong diluent volume.

‖ Seger et al. 2012[41]. Results presented for manual preparation only. Wrong dose and wrong diluent were reported as a combined value in the original article.
*** Yin et al. 2016[55]. One preparation out of 122 was subcutaneous rather than IV. Denominator for concentration errors is IV preparations only.
††† Tavakoli-Ardakani et al. 2013[47]. This study reported that additional data was collected by error subcategory; however, these data are not present in the available publication.
Unless otherwise noted, all data reported from interventional studies are from the baseline period only.

FR, France; GER, Germany; ICU, intensive care unit; PSU, post-surgical unit; TOE, total opportunities for error; UK, United Kingdom

The error subtype of wrong drug selection was infrequent,[3, 25, 28, 31, 37, 41, 44, 45, 54, 55] with the highest reported rate of 4.7% of total doses.[31] Selection of a wrong diluent solution was reported to have occurred in 9 of 34 publications (26%), with results varying across studies (~0% to 49.0%).[3, 28, 32, 37, 39, 44, 46, 53, 54] Of note, the multicenter, multinational study by Cousins et al[28] reported that 1.0% to 49.0% of doses administered had been prepared with an incorrect diluent across all study sites. This range is wider than that of the other included studies (0% to 16.0%). Labeling errors were reported in 6 publications (18%), with reported incidence varying substantially, ranging from 0% to 99.0% (20.0% to 99.0% within the study by Cousins et al[28] and 0% to 91.8% in the study by van den Heever et al study[57]).[28, 31, 37, 43, 55, 57]

Eleven publications (32%) captured incidence of wrong dose, and while most of these studies reported incidence rates below 10%,[25, 28, 32, 33, 44, 45, 48, 51, 54, 55] 1 study did report an incidence rate over 32%.[31] Wrong drug concentration errors were reported in 10 publications (29%), with error incidence per total number of IV doses prepared ranging from 0.3% to 88.6%.[27, 30, 36, 38, 41, 42, 51, 53, 55, 56] While some studies defined a concentration error based on a threshold of a 5%[30, 36, 41] or 10%[30, 36, 38, 51, 55] deviation between the prepared dose and the ideal dose, the study by Castagne et al used a higher threshold of 20%.[27]

Eight studies (24%) reported errors pertaining to wrong diluent volume,[3, 28, 33, 37, 39, 42, 46, 54] with half explicitly defining this error subgroup as any deviation from manufacturer or accepted institutional guidelines for IV preparation.[3, 37, 39, 46] The highest-reported error rate (49.0%) was identified by Niemann and colleagues,[46] while the lowest-reported incidence (0.6%) was from a study by Reece et al.[54]

Reported challenges with aseptic technique included general aseptic technique deviations, bacterial contamination, failure to disinfect the vial, and improper hand hygiene. In studies that reported general inadequate aseptic technique deviations, 3 studies reported incidence rates below 5% (range: 0% to 3.3%)[29, 44, 53]; however, the study by Bertsche and colleagues[26] reported an incidence rate of just under 70% and findings from Helder et al indicated a 92.7% nonadherence rate to hygiene protocols.[52] The variation in incidence rates presented may be the result of differences in error definitions, as Bertsche and colleagues assessed aseptic technique deviations as any procedural deviation from local hygiene guidelines[26] and a study by Helder et al required all 5 steps of the hygiene protocol to be followed.[52] The other studies defined aseptic technique errors either based on bacterial cultures[29, 34] or report of syringes left uncapped during the preparation process.[44]

Bacterial contamination errors were reported in 4 studies, with all reporting incidence under 7% (**Table 3**).[29, 34, 49, 57] Four additional studies report error incidence for both failure to disinfect the vial[28, 37, 52, 53] and improper hand hygiene.[28, 37, 53] In particular, the study by Cousins and colleagues[28] presents a wide range of incidence across aseptic technique subtypes (**Table 3**). The study by Cousins et al[28] presented data from 3 separate institutions located in France, Germany, and the United Kingdom, with the incidence of aseptic technique errors from the French institution found to be dramatically lower (4.0% for vial disinfection and 9.0% for hand washing). Of note, the authors attribute this difference to the French institution having undergone a recent update to its aseptic preparation methods protocol due to a prior outbreak of Legionnaire's disease within the facility.[28]

Ten (29%) studies reported an overall incidence of IAPEs that combined multiple error subtypes.[25, 35, 40, 44-48, 50, 55] These studies have diverse error definitions and error detection methods; thus, the error incidence ranges widely (0.07% to 72.9%).

DISCUSSION

This systematic review found that IAPEs are ubiquitous across countries and hospital locations, and that the types of errors observed and reported are diverse. Reported error incidence was found to vary widely not only between settings (central pharmacies or nursing wards) but also within these settings across studies. Variability in error detection methods and definitions applied may contribute to the variation in error rates reported across studies.

This review identified studies conducted in Europe, North America, South America, Asia, and Africa. While different regions, countries, and even individual institutions are likely to have somewhat different standards and practices for IV admixture preparation, differences in methods and terms applied for data collection did not seem to vary any greater between countries than within a single country. In theory, variation among institutions within the same country has the potential to be larger than variation among countries, as local practices may be more flexible than nationally adopted standards. ISMP noted in its 2011 Guidelines for the Safe Preparation of Sterile Compounds that IV admixture preparation practices are complex, and documentation of errors varies widely across the United States.[58] This highlights an important need for national and international consensuses on defining and identifying IAPEs to fully understand the global patient burden.

Some evidence indicates the effect of location and method of IV admixture preparation on the incidence of errors. In particular, error rates appear to be lower when IV preparation takes

place in central pharmacy settings compared with nursing wards, and lower with automated versus manual preparation. Among studies meeting the inclusion criteria for this systematic review, Dehmel and colleagues[30] and Khalili et al[49] directly compared error rates identified from a central pharmacy to those from a nursing ward using consistent IAPE definitions across settings. The study by Dehmel et al reported a markedly higher rate of wrong concentration errors using manual preparation in a nursing ward when compared with automated preparation in a central pharmacy (53% vs 16%, respectively).[30] Khalili and colleagues reported a low rate of bacterial contamination (1.1%) in admixtures prepared on nursing wards, with no instances of contamination in admixtures prepared in central pharmacies, despite use of manual preparation techniques in each setting.[49] Caution should be taken in generalizing this finding, given the limited sample size of 17 preparations in the central pharmacy and 97 on the nursing ward.[49] Thus, while it appears that moving IV admixture preparation away from the site of care and using automated technologies may reduce IAPEs, further empirical studies are required to substantiate this hypothesis.

In the present systematic review of IAPEs, a patchwork of data emerged from the relevant available literature, in part because no single study design or observational technique is ideal for capturing all the aspects of IV admixture preparation that could result in an error. The majority of studies relied on direct observation of the IV admixture preparation process by a trained observer, while other studies used bacterial culture, measurement of the final admixture concentration, incident reports, and cross-checking against a checklist, computed calculation, or other benchmarks. However, certain error subtypes naturally lent themselves to a specific observational technique, such as bacterial culture for assessing bacterial contamination,

laboratory testing for concentration errors, and direct observation for aseptic technique deviations.

The framework used for categorizing IAPEs in this review was developed to facilitate the aggregation of data collected across studies. While inconsistency across reported error definitions precluded additional quantitative aggregation, we hope the classification system used herein is informative to researchers designing future studies, and may help to facilitate more effective standardization of error reporting going forward.

Within IAPE subtypes, the method of error calculation varied in some cases, which impacted the ability to generalize results across studies. The majority of studies reported the incidence as errors per doses prescribed, prepared, or administered. However, 5 (15%) studies reported errors per total opportunities for error[39, 45, 47, 48, 55] and 2 (6%) studies reported errors per total drug-handling processes.[26, 46] While using total opportunities for error or drug-handling processes may be insightful for those wishing to understand and optimize the IV medication use cycle from the user perspective, errors per dose may be a more useful measurement for researchers interested in patient impact and outcomes.

Error definitions were also variable within some error subtypes. For instance, thresholds for determining concentration errors ranged from ±5% variance from the label specification to as high as ±20% variance.[27, 30, 36, 38, 41, 42, 51, 53, 55, 56] Studies reporting IAPE incidence based on a composite of IAPE subtypes were often composed of common elements (eg, wrong drug, wrong concentration), but were sufficiently different that they could not be directly compared. This finding exposes a need for a standardized taxonomy of error subtypes that can be used across a variety of research settings and countries to facilitate meaningful comparisons.

Other factors that may impact error incidence are circumstances, such as either a recent training or sentinel event as described by a study by Cousins et al,[28] when commenting on proportionally lower aseptic technique deviations observed in the French study site. It was suggested that this finding may be attributed to recent staff training and updated guidelines in the French institution included in the study, prompted by a recent outbreak of Legionnaire's disease at that site. This highlights the impact of staff training not only as a source of potential regional or institutional error variation, but also as a means of reducing error rates. Given the short duration between staff training and study implementation, the long-term sustainability of error reduction potentially gained by staff training in the study by Cousins et al was unclear.

In addition to heterogeneous error incidence results, the articles captured in this systematic review used a variety of approaches to measuring the potential burden of patient harm. Several studies used the existing NCC MERP error index[17] to rate and score errors, and the majority of other studies relied on either local clinician opinion or expert panel. As a result, there is a high degree of variability in terms of how the errors are scored and how potential for patient risk is attributed.

Of the 34 studies included in this review, 12 (35%) provided estimates or general assessments for potentially attributable patient harm or clinical relevance for IAPEs,[3, 26, 29, 31, 32, 39-41, 44-46, 48]. Effective and standardized traceability measures are required to link a defect in the admixture process that occurs early within the medication use cycle with later negative patient outcomes. Given the separation in time and physical location between admixture preparation and potential patient physical adverse response, it can be challenging to link potential negative patient outcomes to the admixture/compounding process where unrecognized potential

errors may exist.[12] There is a need for robust study designs that allow for the assessment of the association between specific errors incidences and patient outcomes.

Several limitations were present in this systematic review. Our search strategy targeted the broad medical literature, but inclusion of additional databases, such as the Cumulative Index of Nursing and Allied Health Literature, may have added nursing publications relevant to this topic. While the quality of publications was generally fair, only 5 studies (15%) were deemed to be of good quality in terms of methodology and reporting.[30, 34, 38, 45, 46] Furthermore, the Hawker method of quality ascertainment is generic and may not be best suited to capturing the unique challenges of this research topic. Drawing comparisons between the studies remains difficult due to substantial variations in error definitions. As a result, meta-analysis of the current IAPE literature was not considered appropriate. Lastly, in the majority of studies, documentation of error severity and associated burden of harm was not sufficient to allow for a thorough evaluation of the impact on patient care or the consequences for healthcare facilities.

CONCLUSIONS

This systematic review is the first to categorize IAPEs according to the characteristics of the error and the location and method of IV preparation. It is our hope that future studies may use these categorizations to provide a meaningful framework to assess IAPEs within their procedural context. With improved standardization of IAPE definitions, grouping error subtypes as we have done may facilitate an improved understanding of where errors happen within the IV preparation process and devising solutions to help eradicate them. There is a clear potential burden of harm for patients resulting from IAPEs, and thus a need to continue to optimize the IV preparation process, focusing on improving preparation workflow, designing and implementing preventive strategies, staff training, and implementing process standardization where possible. Future

research should focus on the development of consistent error subtype definitions and a standardized reporting methodology as well as reliable and reproducible methods to track and link risk factors and the burden of harm associated with these errors.

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Data Sharing Statement

As the research presented is a systematic literature review of published data, no additional unpublished data are available.

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Contributors

NH: Concept/design, data analysis/interpretation, critical revision of article, approval of article.

IB: Data interpretation, critical revision of article, approval of article.

T H-T: Concept/design, data interpretation, critical revision of article, approval of article.

PT: Concept/design, data interpretation, critical revision of article, approval of article.

Competing Interests

NH is a former employee and stockholder of Baxter Healthcare Corporation.

IB is an employee and stockholder of Baxter Healthcare Corporation.

T H-T has no relevant competing interests to disclose.

PT is currently under contract to perform other work for Baxter Healthcare Corporation that is unrelated to the current manuscript.

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FIGURE TITLES AND LEGENDS

Figure 1. Intravenous Medication Use Cycle

Figure 2. PRISMA study inclusion flow diagram

IV, intravenous; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

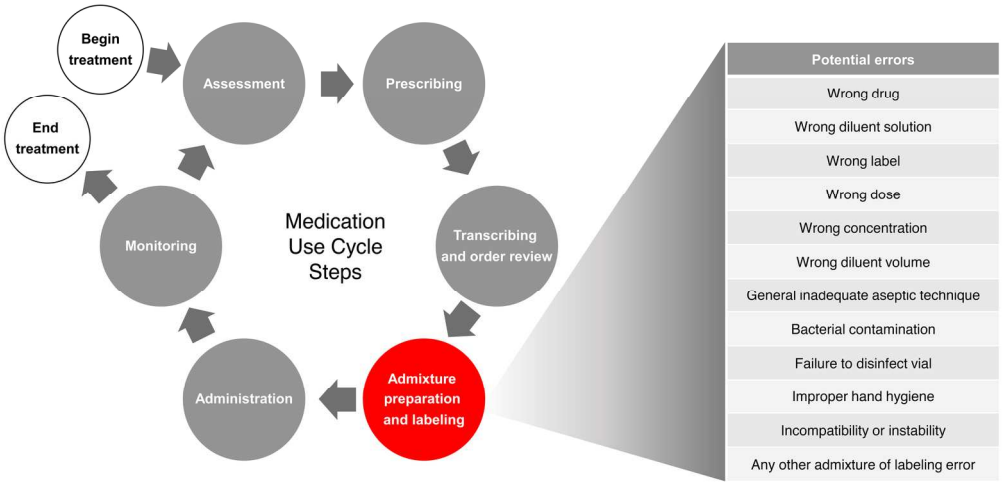

Figure 1. Intravenous medication use cycle

86x41mm (600 x 600 DPI)

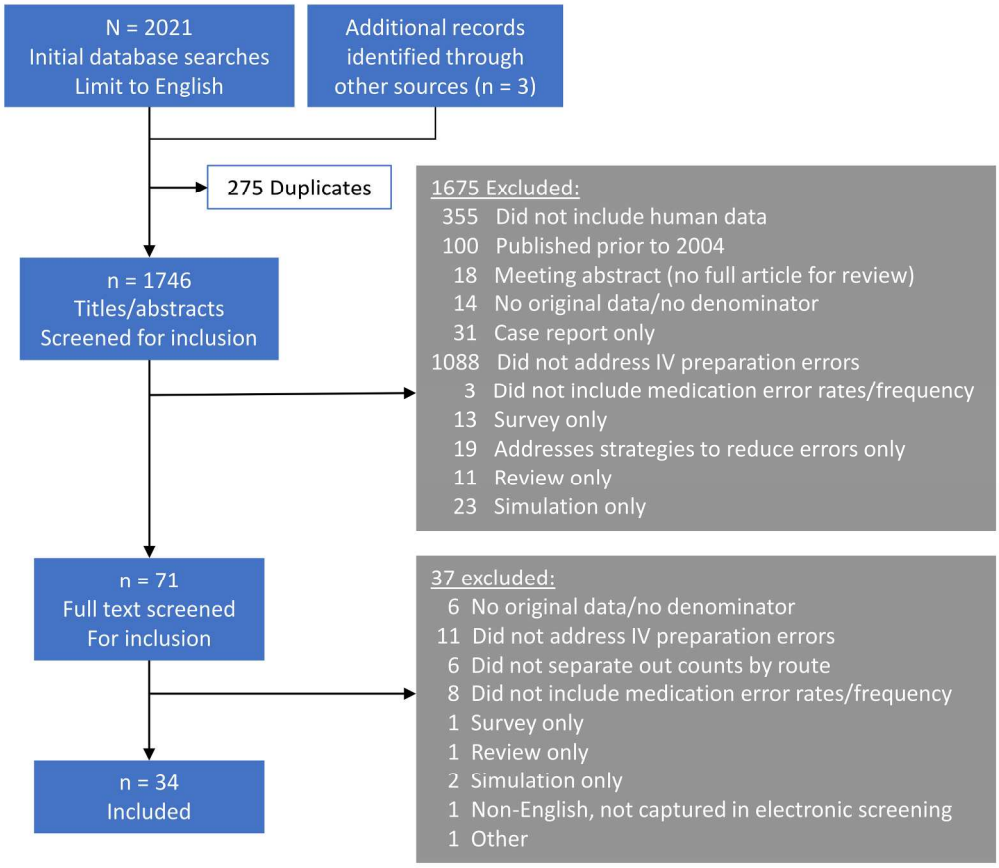

Figure 2. PRISMA study inclusion flow diagram

110x96mm (600 x 600 DPI)

ONLINE SUPPLEMENTARY TABLES

Table S1. Systematic Review Search Terms

Errors	Route of Administration	Compounding	Article Type
([Medication* or drug* or pharmaceutic* or medical or infus*] adj5 error*).mp. OR (Adverse adj5 [event* or reaction*]).mp. OR ([Medication* or drug* or pharmaceutic*] adj5 [contamina* or safety or incompatib*]).mp. OR (Overdos* or over dose*).mp. OR Near miss.mp. OR (incident or incidents or accident*).mp. OR (Steril* or unsteril* or septic or sepsis or aseptic or asepsis).mp. OR ([Healthcare or health care or hospital or bloodstream or blood stream or cross] adj3 infection*).mp. OR patient safety.mp. OR ([Drug or medication* or pharmaceutic*] adj3 [stor*or stability or stable or instability or unstable or expir*).mp. OR ([Wrong* or incorrect* or inappropriate* or error* or	parenteral OR intravenous OR catheter* OR infus* OR iv OR intraocular OR intravitreal OR intramuscular OR subcutaneous OR epidural OR intraosseous OR intraperitoneal OR (ei or im or io or os or ip or iv or pa).fs. use emefd	Compounding OR Compounded OR Reconstitut* OR Admix* OR (Prepar* adj5 (pharmacy or pharmacies or pharmacist or pharmaceutic* or drug* or medication* or ward or wards or nurs* or chemotherapy* or antineoplastic* or cytostatic* or nutrition* or mixture* or solution* or compound or compounds)).mp.	(clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) (EMBASE limits) OR (Evidence based medicine or consensus development or meta-analysis or outcomes research or "systematic review") (EMBASE limits) OR (Clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or observational study or randomized controlled trial or systematic reviews) (Medline limits) OR (Chart review* or observational or systematic or prospective or cohort or retrospective or controlled study or controlled studies or controlled trial* or cross sectional or evidence based or direct observation* or audit or audits or randomized or blind or blinded or case series).mp. (free text terms)

inaccura* or deviation*] adj5 (dose* or dosage* or drug* or medication* or pharmaceutic* or concentration* or diluent* or dilution* or strength* or calculat* or volume or label* or product* or quantit*]).mp. OR (Missing label* or "no label*" or "not label*").mp. OR particulate*.mp.	

Table S2. Details of Hawker Analysis

	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalizability	Implications and Usefulness	Average Score	Overall Quality
Anselmi et al. 2007[1]	2	2	1	3	1	2	2	3	3	**2**	**Fair**
Aruna et al. 2015[2]	2	3	3	3	2	3	3	3	4	**3**	**Poor**
Bertsche et al. 2008[3]	3	3	3	2	1	2	2	2	2	**2**	**Fair**
Campino et al. 2016[4]	2	1	1	1	1	3	1	2	2	**2**	**Fair**
Castagne et al. 2011[5]	2	1	1	3	4	4	1	3	1	**2**	**Fair**
Cousins et al. 2005[6]	1	2	1	3	3	2	2	3	2	**2**	**Fair**
Crill et al. 2010[7]	1	1	1	2	1	1	2	1	2	**2**	**Fair**
Dehmel et al. 2011[8]	1	1	2	3	1	1	2	3	2	**1**	**Good**
Ding et al. 2015[9]	1	2	1	1	2	2	1	3	1	**2**	**Fair**
Fahimi et al. 2007[10]	2	2	2	3	4	2	3	3	1	**2**	**Fair**
Fahimi et al. 2008[11]	1	1	2	3	3	2	2	3	1	**2**	**Fair**
Helder et al. 2016[12]	3	2	1	1	2	2	1	2	3	**2**	**Fair**
Hoefel et al. 2006[13]	2	2	3	1	2	1	2	2	2	**2**	**Fair**

Khalili et al. 2013[14]	2	2	2	3	3	4	2	3	3	**3**	**Poor**
Macias et al 2005[15]	2	1	1	1	1	2	1	1	3	**1**	**Good**
MacKay et al. 2009[16]	2	2	3	4	4	4	3	3	2	**3**	**Poor**
Masini et al. 2014[17]	2	2	3	2	1	4	2	2	3	**2**	**Fair**
Moniz et al. 2014[18]	1	1	2	3	3	4	2	3	3	**2**	**Fair**
Nguyen et al. 2014[19]	1	1	1	2	1	2	1	2	1	**1**	**Good**
Niemann et al. 2015[20]	1	1	1	1	1	2	2	2	2	**1**	**Good**
Ong et al. 2013[21]	2	2	2	3	1	4	2	3	2	**2**	**Fair**
Parshuram et al. 2006[22]	2	2	1	1	1	2	1	2	2	**1**	**Good**
Rashed et al. 2016[23]	1	2	2	3	2	3	1	3	2	**2**	**Fair**
Reece et al. 2016[24]	1	1	1	2	3	3	1	2	2	**2**	**Fair**
Rodriguez-Gonzalez et al. 2012[25]	2	1	1	3	2	2	2	3	2	**2**	**Fair**
Sacks et al. 2009[26]	1	1	1	3	3	1	2	3	2	**2**	**Fair**
Seger et al. 2012[27]	1	2	1	3	1	1	1	3	2	**2**	**Fair**

Skouroliakou et al. 2005[28]	2	2	2	4	4	4	2	3	3	**3**	**Poor**
Tavakoli-Ardakani et al. 2013[29]*	2	3	2	3	2	3	0	3	2	**2**	**Fair**
Terkola et al. 2017[30]	1	1	2	3	4	2	2	3	2	**2**	**Fair**
van den Heever et al. 2016[31]	1	1	1	2	2	3	1	2	1	**2**	**Fair**
Westbrook et al. 2011[32]	2	1	3	3	2	2	2	3	1	**2**	**Fair**
Wheeler et al. 2008[33]	1	3	2	3	1	4	2	3	1	**2**	**Fair**
Yin et al. 2016[34]	2	1	1	2	2	2	1	2	2	**2**	**Fair**

Studies are rated as good (1), fair (2), poor (3), or very poor (4) for each of the Hawker criteria, and given an overall score based on the average rating across all criteria.

*This study could not be fully evaluated due to a missing table in the available publication.

Table S3. Study Characteristics

Study	Geographical Location(s)	Centers, n	Patient Population	Study Design	Observational Technique	Type of Intravenous Admixture	Location of Intravenous Admixture Preparation	Method of Intravenous Admixture Preparation	Patient Impact Measured (Yes / No)
Anselmi et al. 2007[1]	Brazil	3	General inpatient units	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	No
Aruna et al. 2015[2]	India	1	General inpatient units	Single arm	Chart review	Multiple IV therapies	Not specified	Manual	No
Bertsche et al. 2008[3]	Germany	1	General inpatient units and ICU	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes
Campino et al. 2016[4]	Spain	11	NICU	Comparative	Final concentration of admixture	Multiple IV therapies	Central pharmacy vs nursing ward	Manual	No
Castagne et al. 2011[5]	France	1	Oncology inpatients	Single arm	Final concentration of admixture	Chemotherapy	Central pharmacy	Automated	No
Cousins et al. 2005[6]	France Germany UK	3	General medical and surgical inpatients	Single arm	Direct observation (participants in France and Germany were blinded to study purpose)	Multiple IV therapies	Nursing ward	Manual	No
Crill et al. 2010[7]	US	1	Critical care (NICU)	Single arm	Bacterial culture	Intravenous fat emulsion	Central pharmacy	Manual	Yes
Dehmel et al. 2011[8]	Germany	1	Critical care (ICU)	Comparative	Final concentration of admixture	Multiple IV therapies	Central pharmacy vs nursing ward	Automated vs manual	No
Ding et al. 2015[9]	China	1	General surgery inpatients	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes
Fahimi et al. 2007[10]	Iran	1	Critical care (ICU)	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes
Fahimi et al. 2008[11]	Iran	1	Critical care (ICU)	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes

Helder et al. 2016[12]	Netherlands	1	NICU, PICU, and general pediatric wards	Interventional	Direct observation	Multiple IV therapies	Nursing ward	Manual	No
Hoefel et al. 2006[13]	Brazil	1	General units and ICU	Single arm	Direct observation	Antibiotic (cefepime)	Nursing ward	Manual	No
Khalili et al. 2013[14]	Iran	3	Adult and pediatric inpatients	Comparative	Bacterial culture	Multiple IV therapies	Central pharmacy vs nursing ward	Manual	No
Macias et al. 2005[15]	Mexico	1	Critical care (NICU)	Single arm	Bacterial culture	Multiple IV therapies	Nursing ward	Manual	No
MacKay et al. 2009[16]	US	1	Pediatric trauma unit	Interventional	Cross-check	Multiple IV therapies	Central pharmacy	Automated	No
Masini et al. 2014[17]	Italy	1	Inpatient and outpatient oncology	Comparative	Final concentration of admixture	Chemotherapy	Central pharmacy	Automated vs manual	No
Moniz et al. 2014[18]	US	1	Pediatric inpatients	Single arm	Direct observation; Pharmacists reviewed digital photos of each preparation step via a web application	Multiple IV therapies	Central pharmacy	Automated	Yes
Nguyen et al. 2014[19]	Vietnam	1	Critical care (ICU / PSU)	Interventional	Direct observation (participants were blinded to study purpose)	Multiple IV therapies	Not specified	Manual	Yes
Niemann et al. 2015[20]	Germany	1	Pediatric inpatients	Interventional	Direct observation	Multiple IV therapies	Not specified	Manual	Yes
Ong et al. 2013[21]	Malaysia	1	General and acute care, adult and pediatric inpatients	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	No
Parshuram et al. 2006[22]	Canada	1	Pediatric oncology (not specified if inpatient or outpatient)	Single arm	Final concentration of admixture	Chemotherapy	Not specified	Not specified	No
Rashed et al. 2016[23]	UK	1	Pediatric inpatients	Comparative	Direct observation and final concentration of infusion	Morphine	Nursing ward vs operating theater	Manual	No

Reece et al. 2016[24]	US	1	Oncology outpatients	Comparative	Error reports (self-reported and automated)	Chemotherapy	Central pharmacy	Manual	No
Rodriguez-Gonzalez et al. 2012[25]	Spain	1	Gastroenterology inpatients	Single arm	Direct observation (participants were blinded to study purpose)	Multiple IV therapies	Not specified	Not specified	Yes
Sacks et al. 2009[26]	US	1	General adult and pediatric inpatient units and ICU	Single arm	Incident reports	Total parenteral nutrition	Central pharmacy	Automated	Yes
Seger et al. 2012[27]	US	1	Oncology inpatients	Comparative	Direct observation	Chemotherapy	Central pharmacy	Automated vs manual	Yes
Skouroliakou et al. 2005[28]	Greece	1	Neonatal inpatients	Comparative	Cross-check and direct observation	Total parenteral nutrition	Not specified	Automated vs manual	No
Tavakoli-Ardakani et al. 2013[29]	Iran	1	Hematology and oncology inpatients and outpatients	Single arm	Direct observation	Chemotherapy	Nursing ward	Manual	No
Terkola et al. 2017[30]	Austria Czech Republic Denmark Germany Switzerland	10	Oncology	Single arm	Incident reports	Chemotherapy	Offsite pharmacy	Not specified	No
van den Heever et al. 2016[31]	South Africa	1	Obstetric surgery	Single arm	Bacterial culture	Phenylephrine	Obstetric theater	Manual	No
Westbrook et al. 2011[32]	Australia	2	General and surgical inpatients	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	Yes
Wheeler et al. 2008[33]	UK	1	Critical care (neurological) inpatients	Interventional	Cross-check	Multiple IV therapies	Nursing ward	Manual	No
Yin et al. 2016[34]	Malaysia	1	Critical care (ICU)	Single arm	Direct observation	Multiple IV therapies	Nursing ward	Manual	No

Method of preparation was assumed to be manual for studies in which IV admixture preparation occurred in the nursing ward, and no other information regarding method of preparation was provided.
ICU, intensive care unit; IV, intravenous; NICU, neonatal intensive care unit; PSU, post-surgical unit; UK, United Kingdom; US, United States.

Table S4. Patient Burden of Harm

Study	Error Types	Burden of Harm
NCC MERP Medication Error Index Definition of Error Severity		
Fahimi et al. 2007[10]	Wrong drug Wrong label Wrong dose	All observed errors were rated NCC MERP Index Category B ("An error occurred but the error did not reach the patient.")
Rodriguez-Gonzalez et al. 2012[25]	Wrong diluent solution Wrong diluent volume	• Severity was defined according to updated medication errors taxonomy adapted from NCC MERP definitions.[35] • Severity of wrong preparation errors (reconstitution and dilution) were determined to have the potential to cause "no damage."
Sacks et al. 2009[26]	Composite	Severity of errors was defined according to the NCC MERP Index: • 91% of errors did not cause harm (Categories B–D) • 15% of errors were "near misses" (Categories A–B) • 8% of errors contributed to or resulted in temporary harm (Categories E–F) No errors resulted in permanent harm, near death, or death (Categories G–I)
Clinician Assessment or Expert Panel Definition of Error Severity		
Bertsche et al. 2008[3]	Inadequate aseptic technique	• A multidisciplinary committee for quality assurance established risk scores for medical errors. • Errors were assigned a risk score weighted by potential risk of the drug involved and the characteristics of the error (low risk = 0.5, moderate risk = 1, high risk = 2). • Rates of error by severity were reported for all types of administration combined (IV, oral, and gastric tube), but not separately.
Moniz et al. 2014[18]	Wrong dose Wrong drug Wrong diluent solution Inadequate aseptic technique Composite	A new workflow was implemented that detected IV preparation errors that would not have been detected previously. These new errors (n = 447) were rated: • Little potential for harm: 62.64% • Potential ADE with moderate harm: 32.66% • Potential ADE with severe harm: 4.70%
Nguyen et al. 2014[19]	Wrong drug	Clinical relevance of each dose with ≥ 1 error was rated on a validated scale ranging from 0 (no harm) to 10 (death) by a panel of healthcare providers, and was categorized as follows: • Minor outcome: 0–2

Table S4. Patient Burden of Harm

Study	Error Types	Burden of Harm
	Wrong dose	• Moderate outcome: 3–7 • Severe outcome: 8–10 Moderate and severe outcomes were considered clinically relevant (57.9% to 64.0% of errors across the 2 study wards).
	Composite	
Niemann et al. 2014[20]	Wrong diluent solution	Clinical relevance of error subcategories was rated by an expert panel on a four-point scale: 1. No clinical relevance 2. Minor clinical relevance
	Wrong diluent volume	3. Clinical relevance 4. High clinical relevance The frequency of each level of severity combined oral and IV drug errors.
	Composite	
Seger et al. 2012[27]	Wrong drug	• Severity was rated as life-threatening, severe, significant, or little-to-no harm. • Events with potential for little-to-no harm were not included in the analysis. • There were no potentially life-threatening events, and the remaining events were approximately evenly distributed between significant and serious.
	Wrong concentration	Doses with ±5% to 10% variance were considered to have little to no potential for harm. Those with variance > ±10% were rated serious and potentially harmful.
Westbrook et al. 2011[32]	Wrong drug	• Severity was rated on a scale from 1 ("Incident is likely to have little to no effect on the patient") to 5 ("Incident is likely to lead to death"), with ratings of 1 to 2 considered minor errors and 3 to 5 considered serious errors. • 25.5% of overall errors were rated as serious.
	Wrong diluent solution	• 23.8% of wrong diluent solution errors were rated as serious.
	Wrong diluent volume	• 17.4% of wrong diluent volume errors were rated as serious.
Other Method for Determination of Error Severity		
Crill et al. 2010[7]	Inadequate aseptic technique Bacterial contamination	• Severity of errors was not rated. • Authors noted that no cases of systemic infection arose from syringes that had positive cultures.
Ding et al. 2015[9]	Wrong dose	• An error was considered clinically important if it concerned a drug listed in the ISMP list of high-alert medications (2008). • 81% of TPN dose errors involved ISMP high-alert medications.

Table S4. Patient Burden of Harm

Study	Error Types	Burden of Harm
Fahimi et al. 2008[11]	Composite Wrong diluent solution Wrong dose	An error was considered clinically important if it concerned a drug listed in the ISMP list of high-alert medications (2008). There was no severity rating system, but the authors note that none of the errors identified resulted in adverse effects or major risks to patients.

ADE, adverse drug event; ISMP, Institute for Safe Medication Practices; IV, intravenous; NCC MERP, National Coordinating Council for Medication Error Reporting and Prevention; TPN, total parenteral nutrition.

Table S5. Error Incidence Definitions

Admixture Preparation and Labeling Error Types	Definitions	Study
Component Error		
Wrong Drug	An IV drug was prepared or administered that differed from the one that was prescribed	Anselmi et al. 2007[1] Cousins et al. 2005[6] Moniz et al. 2014[18] Nguyen et al. 2014[19] Ong et al. 2013[21] Reece et al. 2016[24] Seger et al. 2012[27] Westbrook et al. 2011[32]
	An unauthorized IV drug was administered, or an order was changed, that was not found in the patient chart	Fahimi et al. 2007[10]
	An incorrect drug or dosage form was selected	Yin et al. 2016[34]
Wrong Diluent Solution	An IV drug was prepared or administered with a diluent that was not compatible with drug and volume to achieve the correct concentration	Cousins et al. 2005[6]
	An IV drug was prepared with the incorrect diluent based on any of the following: • The manufacturer's instructions • Published drug preparation handbooks • Other internal or external drug preparation guidelines	Fahimi et al. 2008[11] Niemann et al. 2015[20] Ong et al. 2013[21] Westbrook et al. 2011[32]
	An IV drug was prepared with the incorrect diluent	Moniz et al. 2014[18] Rashed et al. 2016[23] Reece et al. 2016[24]
	The IV medication was reconstituted or diluted incorrectly according to medication errors taxonomy adapted from NCC MERP definitions [Otero Lopez 2008]	Rodriguez-Gonzalez et al. 2012[25]
Wrong label	An IV drug was prepared or administered with a missing or incomplete label with respect to drug name, dose, patient name, or preparation time	Cousins et al. 2005[6]
	The administration rate, patient identification, date, or time of infusion was not properly documented	Fahimi et al. 2007[10]
	The IV drug label was incomplete with respect to patient, drug, dose, or preparation time, or the opened diluent vials were improperly labeled	Ong et al. 2013[21]

	Syringes or drug infusion containers were not labeled properly	Yin et al. 2016[34]
	Label was incomplete or incorrect with regard to name of solution, concentration of solution, date of preparation, time or preparation, or healthcare worker's signature	van den Heever et al. 2016[31]
	The syringe label was illegible or missing the drug name, dose, concentration, diluent, patient name, patient location, preparer's initials, countersigned, date, or time	Wheeler et al. 2008[33]
Dose or Calculation Error		
Wrong Dose	An incorrect IV drug dose or infusion volume was prepared or administered	Anselmi et al. 2007[1] Cousins et al. 2005[6] Fahimi et al. 2007[10] Hoefel et al. 2006[13] Moniz et al. 2014[18] Reece et al. 2016[24]
	The calculated concentration deviated by >10% of that prescribed	Campino et al. 2016[4]
	An ingredient deviated > ±10% from the correct volume or concentration, a dose was omitted, or an extra dose was given	Ding et al. 2015[9]
	An IV drug that differed by ±10% of the prescribed dose was prepared	Nguyen et al. 2014[19]
	An incorrect dose or diluent volume was calculated that differed from the manufacturer's instructions or published drug preparation handbooks	Fahimi et al. 2008[11]
Wrong Concentration	The sampled IV drug preparation deviated by ±20% or more from its intended concentration	Castagne et al. 2011[5]
	The sampled IV drug preparation deviated by ≥ ±5% or ≥ ±10% from its intended concentration	Dehmel et al. 2011[8] Masini et al. 2014[17]
	The sampled IV drug preparation deviated by ±10% or more from its intended concentration	Parshuram et al. 2006[22]
	The sampled IV drug preparation deviated by more than ±10% from its intended concentration	Campino et al. 2016[4] Yin et al. 2016[34]
	The morphine infusion deviated from its target concentration beyond the pharmacopoeial limit for drug content of morphine sulphate injection (92.5–107.5%)	Rashed et al. 2016[23]
	The sampled IV drug preparation deviated by ±5% or more from its intended concentration	Seger et al. 2012[27]
	The concentration of any of the individual components of total parenteral nutrition was calculated incorrectly	Skouroliakou et al. 2005[28]
	The volume of the sampled IV drug preparation exceeded the gravimetric software's preset tolerance limit • Tolerance levels were set by each site and ranged from 2.5–6%	Terkola et al. 2017[30]

Wrong Diluent Volume	An incorrect diluent volume was used	Cousins et al. 2005[6] Hoefel et al. 2006[13] Reece et al. 2016[24]
	An IV drug was prepared with an incorrect diluent volume based on any of the following: • The manufacturer's instructions • The corresponding summaries of product characteristics • Published drug preparation handbooks • Other internal or external drug preparation guidelines	Niemann et al. 2015[20] Ong et al. 2013[21] Westbrook et al. 2011[32]
	The IV medication was reconstituted or diluted incorrectly according to medication errors taxonomy adapted from NCC MERP definitions [Otero Lopez 2008]	Rodriguez-Gonzalez et al. 2012[25]
	The total volume of the IV solution was incorrect	Skouroliakou et al. 2005[28]
Aseptic Technique Error		
Inadequate Aseptic Technique	The IV drug was not prepared in accordance with local hygiene guidelines	Bertsche et al. 2008[3]
	Sampling of repackaged syringes resulted in positive bacterial cultures	Crill et al. 2010[7]
	Nonadherence to 1 or more of the following hygiene protocols: • Hand disinfection by applying hand alcohol • Rubbing hands for 30 seconds • Using sterile gloves • Disinfecting the ampoule • Allowing the ampoule to dry for 30 seconds	Helder et al. 2016[12]
	Aseptic technique was not followed during IV infusion preparation	Rashed et al. 2016[23] Yin et al. 2016[34]
	Needles or syringes were left uncapped during IV preparation	Moniz et al. 2014[18]
Bacterial Contamination	Sampling of IV drug preparations resulted in positive bacterial cultures	Crill et al. 2010[7] Khalili et al. 2013[14] Macias et al. 2005[15] van den Heever et al. 2016[31]
Failure to Disinfect Vial	Vial top or ampoule was not disinfected during preparation	Cousins et al. 2005[6] Helder et al. 2016[12] Ong et al. 2013[21] Rashed et al. 2016[23]

Improper Hand Hygiene	Hands were not washed, gloves were not worn, or nonsterile gloves were worn during IV drug preparation	Cousins et al. 2005[6] Ong et al. 2013[21]
	Gloves were not worn during IV infusion preparation	Rashed et al. 2016[23]
Composite Error		
Any Admixture or Labeling Error	An IV drug dose was prepared or administered differently from how it was prescribed by the physician in the patient's medical record with regard to: • Wrong patient • Wrong drug • Wrong dose • Omitted dose	Anselmi et al. 2007[1]
	An IV drug was incorrectly formulated or manipulated before administration: • Incorrect reconstitution or dilution • Physicochemical incompatibility of drugs mixed in the same container • Wrong pharmaceutical form	Aruna et al. 2015[2]
	Any of the following IV preparation or administration errors occurred: • Unordered drug • Omitted drug • Wrong dose • Extra dose • Wrong route of administration	Ding et al. 2015[9]
	A drip compounding error of greater than 1 standard deviation from the calculated value for each component in parenteral nutrition preparations occurred	MacKay et al. 2009[16]
	IV drug preparations in the institution were prepared and verified using an IV workflow manager system. Doses that were reworked or rejected were retrospectively reviewed for errors in: • Preparation • Aseptic technique • Documentation	Moniz et al. 2014[18]
	Any IV of the following IV preparation or administration errors occurred: • Wrong drug • Wrong dose • Wrong dosage form • Deteriorated drug • Wrong preparation technique • Omission • Unordered drug • Wrong administration technique	Nguyen et al. 2014[19]
	At least 1 deviation from internal or external drug preparation or administration guidelines, corresponding summaries of product characteristics, or manufacturer recommendations occurred during the drug handling processes (eg, preparation, storage, labeling)	Niemann et al. 2015[20]

	Documented events in parenteral nutrition preparation or administration: • Dose omission • Extra dose • Prescription or refill delayed • Drug list incorrect • Monitoring error • Unauthorized drug • Inadequate pain management • Wrong events (eg, dose, drug, time, patient)	Sacks et al. 2009[26]
	A drug was prepared using the incorrect diluent or incorrect volume, or was not mixed properly	Yin et al. 2016[34]
	A deviation in handling, preparation, or administration of an IV drug occurred based on: • The manufacturer's instructions • *Handbook on Injectable Drugs*, 15th ed. • *Drug Information Handbook*, 19th ed. • American Society of Health-System Pharmacists Drug Information • *Oncology Nursing Drug Handbook*	Tavakoli-Ardakani et al. 2013[29]
IV, intravenous; NCC MERP, National Coordinating Council for Medication Error Reporting and Prevention		

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	10
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	41-43
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	13-16
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	26
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	30
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	30
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	31

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