

## OPEN

# Systemic Causes of In-Hospital Intravenous Medication Errors: A Systematic Review

Sini Kuitunen, MSc (Pharm),\*† Ilona Niittynen, MSc (Pharm),†  
Marja Airaksinen, PhD (Pharm),† and Anna-Riia Holmström, PhD (Pharm)\*†

**Objectives:** Delivery of intravenous medications in hospitals is a complex process posing to systemic risks for errors. The aim of this study was to identify systemic causes of in-hospital intravenous medication errors.

**Methods:** A systematic review adhering to PRISMA guidelines was conducted. We searched MEDLINE (Ovid), Scopus, CINAHL, and EMB reviews for articles published between January 2005 and June 2016. Peer-reviewed journal articles published in English were included. Two reviewers independently selected articles according to a predetermined PICO tool. The quality of studies was assessed using the GRADE system and the evidence analyzed using qualitative content analysis.

**Results:** Eleven studies from six countries were included in the analysis. We identified systemic causes related to prescribing (n = 6 studies), preparation (n = 6), administration (n = 6), dispensing and storage (n = 5), and treatment monitoring (n = 2). Administration, prescribing, and preparation were the process phases most prone to systemic errors. Insufficient actions to secure safe use of high-alert medications, lack of knowledge of the drug, calculation tasks, failure in double-checking procedures, and confusion between look-alike, sound-alike medications were the leading causes of intravenous medication errors. The number of the included studies was limited, all of them being observational studies and graded as low quality.

**Conclusions:** Current intravenous medication systems remain vulnerable, which can result in patient harm. Our findings suggest further focus on medication safety activities related to administration, prescribing, and preparation of intravenous medications. This study provides healthcare organizations with preliminary knowledge about systemic causes of intravenous medication errors, but more rigorous evidence is needed.

**Key Words:** patient safety, medication safety, intravenous medications, medication errors, systemic cause, risk management, systematic review

(*J Patient Saf* 2021;17: e1660–e1668)

Intravenously administered drugs are associated with the highest medication error frequencies and more serious consequences to the patient than any other administration route.<sup>1–3</sup> The bioavailability of intravenously administered medication is high, therapeutic dose range is often narrow, and effects are hard to undo. Many intravenously administered drugs are high-alert medications, bearing a heightened risk of causing significant patient harm if used in

error.<sup>4</sup> For example, in intensive care, the most serious medication errors are associated with intravenously administered high-alert medications, such as catecholamines, insulin, electrolytes, opioids, and parenteral nutrition.<sup>5,6</sup>

Intravenous medication administration is a multistep process involving specific administration devices, information systems and many healthcare professionals with different work tasks and skills. This complex delivery process poses to safety risks if appropriate systemic defenses are not in place.<sup>7–10</sup> Identification of the systemic causes of medication errors (e.g., the possibility to make mistakes in infusion pump programming or confusion between similar drug names and packages) highlights the weaknesses of current intravenous medication practices. This enables the development of medication processes by implementation of effective systemic defenses to prevent medication errors (e.g., smart infusion pumps with error-reduction software or effective means to prevent confusion between similar drug names and packages).

However, the systemic causes of errors throughout the intravenous medication process have not been systematically reviewed. Previous systematic reviews have focused on types and incidence of intravenous medication errors<sup>8</sup> or the effectiveness of smart infusion pumps as a systemic defense.<sup>11</sup> These studies present important knowledge of the frequency of errors and effectiveness of a systemic defense, but they do not focus on medication safety issues throughout the in-hospital intravenous medication process. The aim of our study was to explore recent evidence of systemic causes of in-hospital intravenous medication errors to inform medication safety improvement activities.

## METHODS

### Study Design

A systematic review of recent evidence on systemic causes of in-hospital intravenous medication errors was carried out following the PRISMA guidelines for undertaking and presenting systematic reviews.<sup>12</sup> The quality of included studies was assessed according to the GRADE system.<sup>13</sup> The included articles were analyzed using qualitative content analysis.<sup>14,15</sup>

### Search Strategy

A systematic literature search was performed in June 2016 on MEDLINE (Ovid), Scopus, CINAHL, and EBM reviews covering the period from January 2005 to June 2016. This period was chosen to focus on the most recent evidence published in peer-reviewed journals. An example of the search strategy is presented in Table 1.

We divided the search terms into two themes (“intravenous medication therapy” and “medication errors”), both of which needed to appear in the included articles. The theme “medication error” was chosen according to our study objectives to explore preventable adverse drug events, which occur as a consequence of errors in the medication process caused by omissions or commissions.<sup>3,16</sup> The search strategy was completed with other terms

From the \*HUS Pharmacy, Hospital Pharmacy of Helsinki University Hospital (HUS), Finland; and †Clinical Pharmacy Group, Faculty of Pharmacy, University of Helsinki, Finland.

Correspondence: Sini Kuitunen, MSc (Pharm), HUS Pharmacy, Hospital Pharmacy of Helsinki University Hospital (HUS), Stenbäckinkatu 9, FI00029, HUS, Helsinki, Finland. (e-mail: sini.kuitunen@hus.fi).

S.K. had a PhD research grant from the University Pharmacy (Yliopiston Apteekki), which is a pharmacy corporation owned by the University of Helsinki, Finland. The other authors disclose no conflict of interest.

Supplemental digital contents are available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site ([www.journalpatientsafety.com](http://www.journalpatientsafety.com)).

Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**TABLE 1.** Search Strategy for the MEDLINE (Ovid)

1. Infusions, intravenous/or injections, intravenous/
2. Intravenous\*
3. Infusion\* adj3 drip\*
4. 1 or 2 or 3
5. Medication errors/
6. Medication\* adj3 error\*
7. Administration\* adj3 error\*
8. Prescribing\* adj3 error\*
9. Dispensing\* adj3 error\*
10. Drug\* adj3 error\*
11. Drug\* adj3 mistake\*
12. Drug\* adj3 mishap\*
13. Medication\* adj3 mistake\*
14. Medication\* adj3 mishap\*
15. Administration\* adj3 mistake\*
16. Dispensing\* adj3 mistake\*
17. Prescribing\* adj3 mistake\*
18. Wrong\* adj3 drug\*
19. Wrong\* adj3 dose\*
20. Incorrect\* adj3 drug\*
21. Incorrect\* adj3 dose\*
22. Incorrect\* adj3 administration\* adj3 route\*
23. Drug\* adj3 death\*
24. Medication\* adj3 safety\*
25. Medication\* adj3 event\*
26. Medication\* adj3 incident\*
27. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 4 and 27
29. Limit 28 to English
30. Publication 2005 to current

similar to medication error (Table 1), as inconsistency in terminology and definitions related to medication errors is widely known.<sup>17</sup> A combination of themes “adverse drug event” and “intravenous” was also considered. It was not included to the final search strategy, because the combination resulted to significantly wider amount of citations with the emphasis on drug safety and adverse drug reactions without the objective on medication safety and medication use process. We supplemented the search with a manual search of the reference lists of the included articles to identify all relevant publications.

**Inclusion and Exclusion Criteria**

We applied a predetermined PICO tool (participants, interventions, comparison, and outcomes) to select studies for inclusion.<sup>12</sup> A study was included if participants were hospitalized patients or the study used a patient scenario in a simulated hospital environment, and patients received intravenous medication. We decided to exclude studies conducted in ambulatory settings, such as home infusion chemotherapy, because we wanted to focus on in-hospital intravenous medication process. We also excluded studies focusing on multiple administration routes, if the findings related to intravenous administration route could not be reliably identified and extracted from the results. Comparison was not required. Studies applying measures associated with systemic causes resulting in medication errors or assessment of a system defense to prevent medication errors were included. Studies exploring unpreventable

adverse drug events or only incidence and types of medication errors were excluded. Only English language articles were included. Peer-reviewed journal articles using all methods and study designs were included.

**Study Selection**

After the removal of duplicates, the search produced 1417 potentially relevant publications (Fig. 1). Two reviewers (S.K., I.N.) independently selected studies based on the titles. In case of disagreement, the article was included in the next phase in which the reviewers (S.K., I.N.) independently selected studies based on the abstracts. Disagreements were resolved through discussion and consensus with a third reviewer (A.R.H.). The reviewers (S. K., I.N.) independently selected studies based on full texts of the remaining publications. The articles fulfilling inclusion criteria by both reviewers were included (n = 36). Disagreements were resolved through discussion and consensus with the third reviewer (A.R.H.), which led to the inclusion of nine more articles. A total of 45 publications met the inclusion criteria. After this, reference lists of the included articles were searched manually for relevant articles (n = 12), giving us a total of 57 included studies.

We identified two major themes among the selected articles: systemic causes of in-hospital intravenous medication errors and systemic defenses to prevent errors (Fig. 1). The articles focusing on systemic causes of intravenous medication errors (n = 11) are reported in this publication. Articles focusing on systemic defenses to prevent intravenous medication errors are discussed in another publication.

**Data Extraction and Analysis**

Data extraction and analysis were carried out by one of the authors (S.K.), and the results were carefully reviewed by the other authors (I.N., A.R.H., M.A.). Study characteristics, country and setting, objectives, study design, materials and methods, key findings, and quality of evidence were extracted to a table (Supplementary File 1, <http://links.lww.com/JPS/A243>). We assessed the quality of evidence using the GRADE system, which has the following four levels of evidence: very low, low, moderate, and high.<sup>13</sup> Evidence from randomized controlled trials (RCTs) was graded as high quality and evidence that included observational data was graded as low quality. Factors that decreased the quality of evidence (e.g., study limitations and inconsistency of results) or increased the quality of evidence (e.g., large magnitude of effect) were also taken in account. Measures used in the articles concerning systemic causes of in-hospital intravenous medication errors were extracted to Table 2.

We analyzed the contents of the included articles using qualitative content analysis to identify systemic causes, examples of errors, and suggested systemic defenses for error prevention (Table 3).<sup>10,14,15</sup> We used Leape’s classic analysis of medication errors as a foundation of our taxonomy.<sup>10</sup> Because of the fast development in medication safety research during the past decades and the most important medication safety issues arising from the studies included in our systematic review, we had to make some modifications to the categorizations (Table 3, Table 4). Because we wanted to identify the most crucial systemic risk factors causing errors in the intravenous medication process, we defined a systemic cause as a system failure or an iterative error-prone process step or task, which can be replaced with safer system modifications (e.g., calculation tasks related to preparation can be removed by using standard concentrations of prefilled syringes). The findings were extracted and classified according to the error type and medication process stage, in which the error happened or could have been prevented.

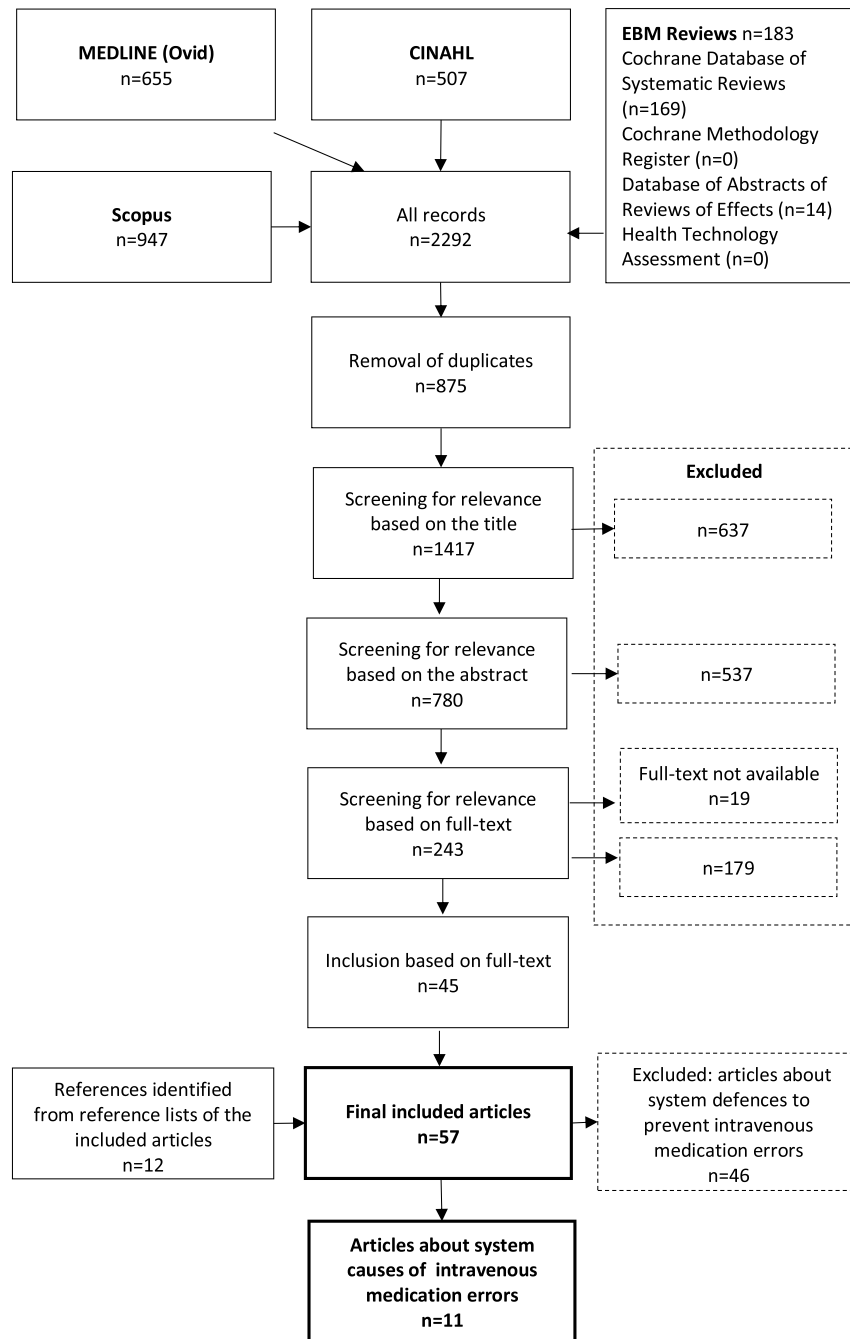


FIGURE 1. Flowchart of the study.

The systemic causes affecting more than one process stage were identified and presented in Table 4.

## RESULTS

### Characteristics of the Included Studies (n = 11)

This systematic review is based on 11 peer-reviewed original articles (Supplementary File 1, <http://links.lww.com/JPS/A243>). The studies were conducted in the United Kingdom (n = 4),<sup>18,25,27,28</sup> United States (n = 3),<sup>19–21</sup> Spain,<sup>26</sup> France,<sup>22</sup> Republic of Korea,<sup>23</sup> and Canada.<sup>24</sup> All studies were carried out in

hospital setting. Three studies were conducted in neonatal intensive care units<sup>20,26,27</sup> and three in adult oncology.<sup>22,24,25</sup>

All of the included studies applied an observational study design (Supplementary File 1, <http://links.lww.com/JPS/A243>). Four of the studies were retrospective analyses of medication error reports,<sup>19–21,25</sup> three were observational studies involving analyses of infusion concentrations,<sup>26–28</sup> two were interview studies,<sup>18,23</sup> one was a prospective analysis of medication orders,<sup>22</sup> and one was a direct observation study.<sup>24</sup> The three studies investigating infusion concentrations to detect preparation errors<sup>26–28</sup> used a controlled study design. More than one error detection method was used in two studies, of which one combined a video

**TABLE 2.** Measures Used to Identify and Describe Errors in the Included Studies (N = 11)

Measures used in more than one study	<p><i>Systemic causes of errors (n = 8 studies)</i></p> <ul style="list-style-type: none"> <li>• Actual or potential causes of errors (n = 7)<sup>18–24</sup></li> <li>• The principal defense(s) that had been breached by each incident (n = 1)<sup>25</sup></li> </ul> <p><i>Concentration accuracy of prepared infusion solution (n = 3)</i></p> <ul style="list-style-type: none"> <li>• Identification of calculation errors and accuracy errors based on the amount of concentration deviation<sup>26</sup></li> <li>• Solution prepared in ward versus pharmacy<sup>27</sup></li> <li>• Individual concentrations of potassium and magnesium measured at regular intervals during infusions<sup>28</sup></li> </ul> <p><i>Contributing factors to medication errors (n = 3)<sup>18–20</sup></i></p> <p><i>Measures related to characteristics of errors (n = 6)<sup>18–22,25</sup></i></p> <ul style="list-style-type: none"> <li>• Severity of errors (n = 5): NCC MERP Index for Categorizing Medication Errors,<sup>19–21</sup> validated scale at four levels,<sup>22</sup> assessment of the degree of actual harm<sup>25</sup></li> <li>• Error type (n = 5)<sup>18–22</sup></li> <li>• Process phase in which the error occurred (n = 2)<sup>19,25</sup></li> </ul>
Measures used in only one of the included studies	<p><i>Measures related to the time of the error:</i> day of the week,<sup>20</sup> time of error,<sup>20</sup> year in which the incident occurred<sup>25</sup></p> <p><i>Measures related to error consequences:</i> actions taken after the error,<sup>19</sup> level of care rendered as a result of the error<sup>19</sup></p> <p><i>Other measures:</i> drugs involved in the error,<sup>19</sup> physical location of the error,<sup>19</sup> the staff involved in the initial error,<sup>19</sup> the sex and age of the patient involved,<sup>19</sup> problems associated with errors in the administration of high-risk medication via intravenous injections,<sup>23</sup> the overall homogeneity of the infusions quantified by the coefficient of variation<sup>28</sup></p>

NCC MERP, The National Coordinating Council for Medication Error Reporting and Prevention.

analysis of preparation technique and revision preparation protocols with analysis of infusion concentrations,<sup>26</sup> and the other used interviews to complement direct observation.<sup>24</sup> Six studies used self-reporting methods, such as voluntary medication error reporting<sup>19–21,25</sup> and interviews.<sup>18,23</sup> The study limitations were not reported and their influence was not assessed in three studies.<sup>23,27,28</sup> None of the included studies applied RCT design, which is why they were graded as low quality.<sup>13</sup>

The measures used to identify and describe systemic causes of medication errors in the studies varied, but some shared measures were identified (Table 2). Actual or potential systemic causes of errors (n = 7) and the principal systemic defenses that had been breached by each incident (n = 1) were used in studies focusing on a larger scale of errors in multiple process stages. Concentration accuracy of prepared infusion solution (n = 3) was used to identify preparation errors in studies comparing different ways of preparing intravenous medications to identify error risk factors. Three of the studies also focused on contributing factors to medication errors.<sup>18–20</sup>

### Systemic Causes of Medication Errors and Potential Systemic Defenses for Error Prevention

The studies identified systemic causes of intravenous medication errors related to prescribing (n = 6 studies), preparation (n = 6), administration (n = 6), dispensing and storage (n = 5), and treatment monitoring (n = 2) (Table 3). The process stage with the most systemic error causes identified was administration.<sup>18–21,23,25</sup> The manual adjustment of infusion rates for each patient is an especially high-risk task, which can lead to wrong dose errors.<sup>19,20,23</sup> An infusion pump programming error can occur as a consequence of confusion between hours and minutes (e.g., 20 minutes instead of 20 hours),<sup>20</sup> weight and volume (e.g., order 5 mg/10 minutes, programmed 5 mL/10 minutes),<sup>19</sup> decimals (e.g., order 0.5 mL/h, programmed 5.0 mL/h),<sup>19,20</sup> volume and time (e.g., 24 mL instead of 24 minutes),<sup>20</sup> syringe sizes (e.g., 20 mL intended, 30 mL used and programmed),<sup>20</sup> or two medications' infusion rates.<sup>20</sup>

In all of the studies (n = 11), potential systemic defenses for intravenous medication error prevention were suggested (Table 3). Error prevention strategies were presented in discussion sections

of the articles; thus, their effectiveness was not measured. Overall, activities related to process standardization, replacement of error-prone tasks with technological solutions and staff education were suggested to decrease possibilities of errors and improve error detection.<sup>18–28</sup>

Some systemic causes enabled medication errors in more than one process stage (Tables 3, 4). Insufficient actions to secure safe use of high-alert medications<sup>18,23,25</sup> and lack of knowledge of the drug<sup>18,19,24,26–28</sup> were identified as the two causes, which affected the most process stages, followed by calculation tasks<sup>19,21,26</sup> and confusion between look-alike, sound-alike medications (LASAs).<sup>18,19,21,22</sup> The studies also pointed out that absence of a systemic defense, or an existing defense breaking down, can enable errors. For example, failure to review orders after prescribing or to double-check during the preparation and administration stages can let errors actually reach the patient.<sup>18,22,24</sup>

### DISCUSSION

To the best of our knowledge, this is the first systematic review to summarize systemic causes of intravenous medication errors in hospitals. We found a limited number of studies, all of them being observational studies not providing the most rigorous evidence. Current intravenous medication systems remain vulnerable, which can result in patient harm. According to the included studies, administration, prescribing, and preparation are the process phases most prone to systemic errors. We found insufficient actions to secure safe use of high-alert medications and lack of knowledge of the drug two leading error causes in multiple process stages, followed by calculation tasks, failure in double-checking procedures, and confusion between LASA medications.

Considering the issues related to high-alert medications, the Institute for Safe Medication Practices recommends standardizing the ordering, storage, preparation, and administration of high-alert medications and improving access to information about these drugs.<sup>4</sup> Furthermore, healthcare organizations should use multidisciplinary teams to review more carefully and standardize the use processes of high-alert medications through risk management strategies, such as failure mode and effects analysis and root cause analysis of reported errors.<sup>19,20</sup>

**TABLE 3. Systemic Causes of Intravenous Medication Errors and Potential Systemic Defenses for Error Prevention Identified in the Included Studies (N = 11)**

Error Type	Systemic Causes and Examples of Errors	Potential Systemic Defense for Error Prevention
Prescribing (ordering, Wrong drug <sup>22,23</sup> )	transcription and order verification) (n = 6) <sup>18,19,21–23,25</sup> <i>LASA medications</i> : choosing a wrong drug (e.g., a sound-alike drug), confusion with drug name because of verbal prescription <sup>22,23</sup>	Incorporating medical consultation and multidisciplinary reports to CPOE <sup>22</sup> Standardized procedures for high-alert medications and emergencies <sup>23</sup>
Wrong dose <sup>19,21–23</sup>	<i>CPOE and CDSS</i> : not taking CPOE alarms into account, “alarm fatigue,” inaccurate adaptation (e.g., 10 mg/kg instead of 15 mg/kg), weight (e.g., 64 kg instead of 74 kg), or unit (e.g., 3 mg instead of 3 g) <sup>22,23</sup> <i>Communication errors</i> : confusion with dosage because of verbal prescription <sup>23</sup> <i>Calculation tasks</i> : 10-fold errors, failure in dosage conversation <sup>19,21</sup> <i>CPOE and CDSS</i> : the possibility to choose wrong route (e.g., IT instead of IV) <sup>25</sup> <i>Lack of standardization</i> ; <i>CPOE and CDSS</i> : inaccurate date or treatment regimen <sup>22</sup> <i>Lack of knowledge of the drug</i> : failure to adjust dose to comorbidities (e.g., renal impairment, sleep apnea) or other drugs (e.g., opioid and multiple CNS drugs) <sup>19</sup> <i>Lack of patient data</i> : <i>high-alert drugs</i> : PCA to patient unable to use it properly <sup>19</sup>	Pharmacist’s analysis of prescriptions and duplication of previous order in CPOE <sup>22</sup> Standardized procedures for high-alert medications and emergencies <sup>23</sup> Increasing vigilance and adapting alarms to the needs of prescribing physicians <sup>22</sup> Using conversion charts to reduce the need for calculations <sup>21</sup> Documented independent double-checks for calculations <sup>19</sup> Not reported
Wrong route <sup>25</sup>		Standardization of schedules and utilization of CPOE <sup>22</sup>
Extra dose <sup>22</sup>		Full training of practitioners before they participate in high-risk processes (e.g., prescribing PCA) <sup>19</sup>
Wrong choice <sup>19</sup>		
Multiple error types <sup>8,19,22</sup>	<i>CPOE and CDSS</i> : failure in documentation (e.g., wrong patient identity or treatment setting identification, incomplete or illegible prescription, contradictory or duplicated orders, prescription forgotten, or documented in wrong place) <sup>18,19,22</sup> <i>Failure to double-check</i> ; overconfidence, casual attitudes or deciding not to question prescriber (e.g., respected physician, other person not available) <sup>18,22</sup>	Pharmacist’s analysis of prescriptions within the CPOE system <sup>22</sup> System simplification <sup>22</sup> Equal responsibility and empowerment to challenge prescriber <sup>18</sup> Education, training, and increased access to supportive resources <sup>18</sup>
Dispensing and storage (n = 5) <sup>18,19,21,23,25</sup>		“Tall man” lettering to help practitioners visually distinguish between packages <sup>19</sup>
Wrong drug <sup>18,19,21,23,25</sup>	<i>LASA medications</i> : <i>high-alert drugs</i> : e.g., morphine and HYDROMORPHONE or two sound-alike medicine during product shortage, misfills of automated dispensing devices (e.g., wrong concentration or wrong product in machine’s pocket) <sup>18,19,21</sup> <i>High-alert drugs</i> : too easy availability of high-alert medications (e.g., storing IT and IV drugs together or undiluted electrolytes in wards and patient carts) <sup>23,25</sup>	ADD directly linked to pharmacy information systems <sup>19</sup> Not overriding prompts from ADD without consulting a pharmacist <sup>19</sup> Independent double-checks of products by two individuals <sup>19</sup> Separate storage of high-risk route drugs (e.g., IT doses in a locked fridge) <sup>25</sup> Maintaining adequate product inventory for patient care <sup>21</sup> Multiprofessional resolving of differences between products and original order <sup>21</sup>
Preparation (n = 6) <sup>18,19,24,26–28</sup>		Entering only one preparation to the biological safety cabinet at a time <sup>24</sup>
Wrong drug or diluent <sup>18,24</sup>	<i>Similar looking equipment</i> : preparing multiple medications at the same time and storing them in close proximity (e.g., incorrect labeling) <sup>18,24</sup> <i>Lack of knowledge of the drug</i> : incorrect type of diluent for reconstitution <sup>24</sup>	Pairing label and instructions with preparation supplies and final product <sup>24</sup> An independent double-check of diluent type during preparation <sup>24</sup>
Wrong dose <sup>19,24,26–28</sup>	<i>Calculation tasks</i> : no standard concentrations (e.g., other strength of replacement infusion, using standard volumes makes doses unique) <sup>26</sup> <i>Problems related to drug product</i> : larger volume of drug in a vial than stated in the label (e.g., overdose if full ampoule or vial is loaded without checking volume), layering of viscous solutions in the diluent (e.g., electrolyte concentrates) <sup>26,28</sup> <i>Lack of knowledge of the drug</i> : incorrect volume (e.g., wrong syringe size) <sup>24,26,27</sup>	Documented independent double-checks of calculations <sup>27</sup> Implementation of standard concentrations to eliminate calculation errors <sup>26,27</sup> Using bulk solutions prepared aseptically in the pharmacy <sup>27,28</sup> Using right-sized syringe in volume measurements <sup>26,27</sup> Drug manufacturers’ and syringe providers’ compliance with current legislation <sup>26</sup> An independent double-check of diluent volume during preparation <sup>24</sup>
Wrong technique <sup>26–28</sup>	<i>Lack of knowledge of the drug</i> : incorrect mixing or insufficient reconstitution time (e.g., overdose or too low dose because drug was not uniformly distributed in the syringe or infusion bag) <sup>26–28</sup>	Educational interventions about correct preparation technique <sup>26</sup>
Multiple error types <sup>8,24</sup>	<i>Failure to double-check</i> : staff shortage, busy shift, inadequate staff skill-mix, only visual inspecting look-alike products after reconstitution or not checking thoroughly when tasks were carried out with a trusted colleague <sup>18,24</sup>	Using electrolyte solutions prepared commercially or aseptically in pharmacy <sup>28</sup> Vigorous mixing and using bags rather than syringes for electrolyte solutions <sup>28</sup> Equal responsibility and empowerment to challenge prescriber <sup>18</sup> Education, training and increased access to supportive resources <sup>18</sup>
Administration (n = 6) <sup>18–21,23,25</sup>		

Wrong drug <sup>19,23</sup>	<i>LASA medications</i> : similar looking equipment: several injection lines on a single fluid hanger, confusion between LASA medications <sup>19,23</sup>	Barcode medication administration systems <sup>19,23</sup> Independent double-checks of products by two individuals <sup>19</sup> Smart pumps including a drug library and safety-alerts <sup>20</sup> Standardizing infusion pumps (e.g., pumps from a single manufacturer) <sup>20</sup> Documented independent double-checks for right pump settings <sup>19,20</sup> Documented pump inspection and validation of infusion rates at shift change <sup>20</sup> Restricting the number of PCA medications to avoid confusion in drug selection from PCA screen <sup>19</sup> Consult reference material for each drug during setup (e.g., dosing cards) <sup>19</sup> Clear labeling (e.g., drug concentration prominent and clearly legible) <sup>19</sup> Educating staff and family members about proper use of the PCA pump <sup>19</sup> Awareness of the possibility of tubing misconnections, tracing the origin of tubing to insertion or connection to ascertain the proper location of each tube <sup>21</sup> Document infusion pump tubing at shift change <sup>20</sup> Separating two drugs with different routes in time, location and appearance (e.g., IV vinca alkaloids prepared in mini-bags to avoid accidental IT administration) <sup>23</sup> Not reported
Wrong dose <sup>19–21,23</sup>	<i>Calculation tasks</i> : products supplied in different concentrations (e.g., pump not reprogrammed when starting replacement infusion), 10-fold errors, confusion between weight and volume (e.g., 1 mg ordered, 10 mg/mL used, 1 mL given) <sup>19,21</sup> <i>Problems related to drug product</i> : too low dose because more than one ampoule is needed for one dose <sup>21</sup> <i>Infusion device problems</i> : wrong infusion rate because of pump programming error, wrong programming of other PCA pump variables (e.g., bolus dose, lockout interval or basal background infusion rate) <sup>19,21,23</sup> <i>High-alert drugs</i> : patient's family member activating PCA (e.g., overdose risk) <sup>19</sup>	
Wrong route <sup>20,21,23,25</sup>	<i>LASA medications</i> : similar looking equipment: confusion between two routes (e.g., oral syrup given IV), similar tubing or syringes (e.g., unlabelled tubing and syringes, confusing IV line with epidural line, connecting IV line to other lines) <sup>21,23</sup> <i>High-alert drugs</i> : inadequate separation of IT and IV drugs in time or location (e.g., same administration day, storing them together) <sup>25</sup>	
Extra dose <sup>18</sup>	<i>CPOE and CDSS</i> : communication errors: failure to record medication administration, unauthorized drug (e.g., wrong patient or unordered drug) <sup>18</sup>	Documented verification of orders, validation of infusion device settings and trace of infusion pump tubing at shift change <sup>20</sup>
Missed dose <sup>19,20</sup>	<i>Infusion device problems</i> : tubing disconnected or never connected to patient, pump not turned on, interrupted infusion not resumed <sup>19,20</sup> <i>CPOE and CDSS</i> : orders for therapy overlooked <sup>19,20</sup>	Not reported
Equipment failure <sup>20,23</sup>	<i>Infusion device problems</i> : insufficient pump settings (e.g., not allowing infusion <1 mL/h), infusion device shortage, device malfunction <sup>20,23</sup> <i>Lack of knowledge of the drug</i> : removing light-resistant wrapping <sup>23</sup>	
Multiple error types <sup>18</sup>	<i>Failure to double-check</i> : distractions, poor instructions of which things should be checked, not checking thoroughly (e.g., task carried out with a trusted colleague) <sup>18</sup>	Education, training, and increased access to supportive resources <sup>18</sup>
Treatment monitoring (n = 2) <sup>18,23</sup>		
Inadequate monitoring <sup>18,23</sup>	<i>Lack of knowledge of the drug</i> : high-alert drugs: lack of knowledge (e.g., serious adverse effects, high-alert medications), no support resources, or choosing not using them <sup>18,23</sup>	Education, training, and increased access to supportive resources <sup>18</sup> Safety guidelines, evaluation, and education for high-alert medications <sup>23</sup>

Abbreviations: ADD, automated dispensing device; CDSS, clinical decision support system; CPOE, computerized physician order entry; IT, intrathecal; IV, intravenous; LASA, look-alike sound-alike; PCA, patient-controlled analgesia.

**TABLE 4.** The Most Crucial Systemic Causes Resulting in Intravenous Medication Errors in More Than One Medication Process Stage

Systemic Cause	Prescribing	Dispensing and Storage	Preparation	Administration	Treatment Monitoring
Insufficient actions to secure safe use of high-alert medications	X	X		X	X
Lack of knowledge of the drug	X		X	X	X
Calculation tasks	X		X	X	
Failure in double-checking procedures	X		X	X	
Confusion between LASA medications	X	X		X	
Lack of CPOE standardization and ineffectiveness of CDSS	X			X	
Confusion between similar looking equipment (e.g., syringes, infusion bags, tubing)			X	X	
Communication errors	X			X	
Problems related to drug product			X	X	

Abbreviations: CDSS, clinical decision support system; CPOE, computerized physician order entry.

Calculation tasks were identified as a cause of wrong dose errors in multiple medication process stages.<sup>19,21,26</sup> Pediatric and neonatal populations are at the highest risk for life-threatening calculation errors because of weight-based dosing and inadequate commercial products.<sup>21,29,30</sup> Standard concentration procedures are an important way to improve intravenous medication safety.<sup>26,27,31,32</sup> Calculation tasks can also be eliminated or secured by successful implementation of other systemic defenses, such as smart infusion pumps using error-reduction software, dose conversion charts, and decision support systems.<sup>19,29,33</sup> In addition, smart infusion pumps can reduce errors related to manual pump programming, which we identified as a particular high-risk task.<sup>11,31,19,20,23</sup>

Manual independent double-checks are widely used in error identification, but the frequent poor quality of these procedures can enable medication errors.<sup>4,8,18,24,29</sup> Safety of procedures relying on accuracy and awareness of an individual is easily jeopardized. Likewise, procedures that lack sensitivity to all potential error types are problematic.<sup>18,24</sup> Some manual double-checks could relatively simply be replaced with more reliable technological solutions (e.g., barcode scanning) or even eliminated by reducing error-prone process steps (e.g., reducing preparation errors by using pre-prepared syringes or sealed systems requiring minimal manipulation before use).<sup>8,26–28,34,35</sup>

In our study, absence of a standardized order review protocol was identified as a risk factor for inheritance of prescribing errors in later process stages.<sup>18,22</sup> To support safe prescribing, an order review by a clinical pharmacist combined with clinical decision support systems would be an optimal strategy for error reduction.<sup>4,22,29,33,36–38</sup> In addition, confusion between LASA medications can be particularly significant when high-alert medications are involved.<sup>19,23,39,40</sup> To decrease errors related to LASA medications, use of Tall Man lettering (e.g., morphine and HYDROmorphine), safe storage, auxiliary labels, and barcode medication administration systems should be considered.<sup>4,39,40</sup>

Our study was conducted in accordance with the PRISMA checklist.<sup>12</sup> We included only peer-reviewed articles in the analysis and assessed the quality of selected studies using the GRADE system.<sup>13</sup> The literature search was restricted to articles published in English; thus, studies published in other languages were excluded. Although intravenous medications are widely used in hospitals and associated with frequent and particularly serious errors,<sup>1–3</sup> the number of studies included in our systematic review was limited. Many excluded studies focused on incidence and

types of intravenous medication errors, with no emphasis to examine why the errors happened. We also excluded some studies focusing on multiple administration routes, if the findings related to intravenous administration route could not be reliably identified and extracted from the results. We needed to make some modifications to the error categorizations presented in Leape's classic analysis of medication errors,<sup>10</sup> because we wanted to identify the most crucial systemic causes of intravenous errors to inform medication process development in hospitals.

Probably because of our study objectives, none of the included studies applied an RCT design; the data could not be summarized statistically. Only two studies used more than one error detection method, which has been recommended to discover representative information concerning medication errors.<sup>41</sup> Especially self-reporting methods have been associated with lack of representativeness and the issue of underreporting. We also found a lot of variation between study objectives, designs, and measures, which is an area of development. It is probable that administration seems the most complex and error-prone process stage because it was the most widely studied. Especially the evidence related to errors in treatment monitoring was limited. Furthermore, some important areas, such as microbiological contamination related to preparation, were not identified because this was not measured in any of the studies, although it has been recognized as an area of improvement.<sup>42</sup>

In addition to systemic causes of intravenous medication errors, our initial target was to explore contributing factors. However, this was not possible, because contributing factors were explored in only three studies with variable research strategies.<sup>18–20</sup> There is a need for further studies to explore systemic causes of intravenous medication errors in other settings than inpatient care, because intravenous administration, such as home infusion chemotherapy, is becoming more common in ambulatory settings.

## CONCLUSIONS

According to our study, insufficient actions to secure safe use of high-alert medications, lack of knowledge of the drug, calculation tasks, failure in double-checking procedures, and confusion between LASA medications are the leading systemic causes of intravenous medication errors. Current intravenous medication systems remain vulnerable. Our findings suggest further focus on medication safety activities related to administration, prescribing,

and preparation of intravenous medications. Process standardization and implementation of effective systemic defenses are essential to improve medication safety. Our study provides health-care organizations with preliminary knowledge about systemic causes of intravenous medication errors, but more rigorous evidence is needed.

## REFERENCES

- Westbrook JI, Rob MI, Woods A, et al. Errors in the administration of intravenous medications in hospital and the role of correct procedures and nurse experience. *BMJ Qual Saf*. 2011;20:1027–1034.
- Keers RN, Williams SD, Cooke J, et al. Causes of medication administration errors in hospitals: a systematic review of quantitative and qualitative evidence. *Drug Saf*. 2013;36:1045–1067.
- Krähenbühl-Melcher A, Schlienger R, Lampert M, et al. Drug-related problems in hospitals: a review of the recent literature. *Drug Saf*. 2007;30:379–407.
- Institute for Safe Medication Practices. ISMP list of high-alert medications in acute care settings. Available at: <http://www.ismp.org/tools/highalertmedications.pdf>. Published 2018. Accessed November 30, 2018.
- Valentin A, Capuzzo M, Guidet B, et al. Errors in administration of parenteral drugs in intensive care units: multinational prospective study. *BMJ*. 2009;338:b814.
- Thomas AN, Macdonald JJ. A review of patient safety incidents reported as 'severe' or 'death' from critical care units in England and Wales between 2004 and 2014. *Anaesthesia*. 2016;71:1013–1023.
- Taxis K, Barber N. Causes of intravenous medication errors: an ethnographic study. *Qual Saf Heal Care*. 2003;12:343–347.
- McDowell SE, Mt-Isa S, Ashby D, et al. Where errors occur in the preparation and administration of intravenous medicines: a systematic review and Bayesian analysis. *Qual Saf Health Care*. 2010;19:341–345.
- Reason J. Human error: models and management. *BMJ*. 2000;320:768–770.
- Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. *JAMA*. 1995;274:35–43.
- Ohashi K, Dalleur O, Dykes PC, et al. Benefits and risks of using smart pumps to reduce medication error rates: a systematic review. *Drug Saf*. 2014;37:1011–1020.
- Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1–9.
- Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008;336:995–998.
- Elo S, Kyngäs H. The qualitative content analysis process. *J Adv Nurs*. 2008;62:107–115.
- Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res*. 2005;15:1277–1288.
- National Coordinating Council for Medication Error Reporting and Prevention. About medication errors. Available at: <https://www.nccmerp.org/about-medication-errors>. Accessed November 28, 2018.
- Lisby M, Nielsen LP, Brock B, et al. How are medication errors defined? A systematic literature review of definitions and characteristics. *International J Qual Health Care*. 2010;22:507–518.
- Keers RN, Williams SD, Cooke J, et al. Understanding the causes of intravenous medication administration errors in hospitals: a qualitative critical incident study. *BMJ Open*. 2015;5:1–10.
- Hicks RW, Sikirica V, Nelson W, et al. Medication errors involving patient-controlled analgesia. *Am J Heal Pharm*. 2008;65:429–440.
- Hicks RW, Becker SC, Chuo J. A summary of NICU fat emulsion medication errors and nursing services: data from MEDMARX. *Adv Neonatal Care*. 2007;7:299–308.
- Hicks RW, Becker SC. An overview of intravenous-related medication administration errors as reported to MEDMARX®, a national medication error-reporting program. *J Infus Nurs*. 2006;29:20–27.
- Nerich V, Limat S, Demarchi M, et al. Computerized physician order entry of injectable antineoplastic drugs: an epidemiologic study of prescribing medication errors. *Int J Med Inform*. 2010;79:699–706.
- Kim M, Seomun G. Errors in high-risk intravenous injections administered by nurses: the causes according to healthcare professionals. *Heal Sci J*. 2014;8:249–261.
- White R, Cassano-Piché A, Fields A, et al. Intravenous chemotherapy preparation errors: patient safety risks identified in a pan-Canadian exploratory study. *J Oncol Pharm Pract*. 2014;20:40–46.
- Franklin BD, Panesar SS, Vincent C, et al. Identifying systems failures in the pathway to a catastrophic event: an analysis of national incident report data relating to vinca alkaloids. *BMJ Qual Saf*. 2014;23:765–772.
- Campino A, Arranz C, Unceta M, et al. Medicine preparation errors in ten Spanish neonatal intensive care units. *Eur J Pediatr*. 2016;175:203–210.
- Aguado-Lorenzo V, Weeks K, Tunstell P, et al. Accuracy of the concentration of morphine infusions prepared for patients in a neonatal intensive care unit. *Arch Dis Child*. 2013;98:975–979.
- Donaldson TM, Mani V, Wheeler DW. Factors affecting the concentration of electrolyte infusions prepared from stock solutions. *Postgrad Med J*. 2011;87:83–88.
- Ameer A, Dhillon S, Peters M, et al. Systematic literature review of hospital medication administration errors in children. *Integr Pharm Res Pract*. 2015;4:153–165.
- Ghaleb MA, Barber N, Franklin BD, et al. Systematic review of medication errors in pediatric patients. *Ann Pharmacother*. 2006;40:1766–1776.
- Institute for Safe Medication Practices. Proceedings from the ISMP Summit on the Use of Smart Infusion Pumps: guidelines for safe implementation and use. 2009. Available at: <https://www.ismp.org/sites/default/files/attachments/2018-06/ISMP Smart Pump Guidelines 2009.pdf>.
- Larsen GY, Parker HP, Cash J, et al. Standard drug concentrations and smart-pump technology reduce continuous-medication-infusion errors in pediatric patients. *Pediatrics*. 2005;116:e21–e25.
- Manias E, Kinney S, Cranswick N, et al. Interventions to reduce medication errors in pediatric intensive care. *Ann Pharmacother*. 2014;48:1313–1331.
- Evely R, Russell J, Mathew D, et al. Confirming the drugs administered during anaesthesia: a feasibility study in the pilot National Health Service sites, UK. *Br J Anaesth*. 2010;105:289–296.
- Hertig JB, Degnan DD, Scott CR, et al. A comparison of error rates between intravenous push methods: a prospective, multisite, observational study. *J Patient Saf*. 2018;14:60–65.
- Manias E, Williams A, Liew D. Interventions to reduce medication errors in adult intensive care: a systematic review. *Br J Clin Pharmacol*. 2012;74:411–423.
- Bedouch P, Sylvoz N, Charpiat B, et al. Trends in pharmacists' medication order review in French hospitals from 2006 to 2009: analysis of pharmacists' interventions from the Act-IP© website observatory. *J Clin Pharm Ther*. 2015;40:32–40.
- Hermanspann T, Schoberer M, Robel-Tillig E, et al. Incidence and severity of prescribing errors in parenteral nutrition for pediatric inpatients at a neonatal and pediatric intensive care unit. *Front Pediatr*. 2017;5:149.



39. Tyynismaa L, Honkala A, Airaksinen M, et al. Identifying high-alert medications in a university hospital by applying data from the medication error reporting system. *J Patient Saf.* 2017;1–8.
40. Institute for Safe Medication Practices. ISMP's List of Confused Drug Names. Available at: <https://www.ismp.org/sites/default/files/attachments/2017-11/confuseddrugnames%2802.2015%29.pdf>. Published 2011. Accessed November 30, 2018.
41. Härkänen M, Turunen H, Vehviläinen-Julkunen K. Differences between methods of detecting medication errors: a secondary analysis of medication administration errors using incident reports, the global trigger tool method, and observations. *J Patient Saf.* 2016;1–9.
42. Hedlund N, Beer I, Hoppe-Tichy T, et al. Systematic evidence review of rates and burden of harm of intravenous admixture drug preparation errors in healthcare settings. *BMJ Open.* 2017;7:e015912.