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MEDICATION SAFETY IN INTRAVENOUS DRUG ADMINISTRATION:

ERROR CAUSES AND SYSTEMIC DEFENSES IN HOSPITAL SETTING

Sini Kuitunen

DOCTORAL DISSERTATION

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ABSTRACT

Intravenous administration of drugs is associated with the highest medication error frequencies and more serious consequences to the patient than any other administration route. The bioavailability of intravenously administered medication is high, the 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. Smart infusion pumps with dose error-reduction software can be used to prevent harmful medication errors in high-risk clinical settings, such as neonatal intensive care units.

This study investigated intravenous medication safety in hospital settings by identifying recent research evidence related to systemic causes of medication errors (Study I) and systemic defenses to prevent these errors (Study II). The study also explored the development of dose-error reduction software in a neonatal intensive care unit (Study III). A systems approach to medication risk management based on the Theory of Human Error was applied as a theoretical framework.

The study was conducted in two phases. In the first phase, a systematic review of recent research evidence on systemic causes of intravenous medication errors (Study I) and systemic defenses aiming to prevent these errors (Study II) was carried out. In Study I, 11 studies from six countries were included in the analysis. Systemic causes related to prescribing (n=6 studies), preparation (n=6), administration (n=6), dispensing and storage (n=5) and treatment monitoring (n=2) were identified. Insufficient actions to secure safe use of high-alert medications, lack of knowledge of the drug, failures in calculation tasks and 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.

In Study II, 46 studies from 11 countries were included in the analysis. Systemic defenses related to administration (n=24 studies), prescribing (n=8), preparation (n=6), treatment monitoring (n=2), and dispensing (n=1) were identified. In addition, five studies explored defenses related to multiple stages of the medication use process. Defenses including features of closed-loop medication management systems appeared in 61% of the studies, smart pumps being the defense most widely studied (24%). The evidence quality of the included articles was limited, as 83% were graded as low quality, 13% moderate quality, and only 4% high quality.

A mixed-methods study was conducted in the second phase, applying qualitative and quantitative methods (Study III). Medication error reports were used to develop simulation-type test cases to assess the suitability of dosing limits in a neonatal intensive care unit's smart infusion pump drug

library. Of all medication errors reported in the neonatal intensive care unit, 3.5% (n=21/601) involved an error or near-miss related to wrong infusion rate. Based on the identified error mechanisms, 2-, 5-, and 10-fold infusion rates and mix-ups between infusion rates of different drugs were established as test cases. When conducting the pump programming for the test cases (n=226), no alerts were triggered with infusion rates responding to the usual dosages (n=32). Of the erroneous 2-, 5-, and 10-fold infusion rates, 73% (n = 70/96) caused an alert. Mix-ups between infusion rates triggered an alert only in 24% (n=24/98) of the test cases.

This study provided an overview of recent research evidence related to intravenous medication safety in hospital settings. Current intravenous medication systems remain vulnerable, which can result in patient harm. While in-hospital intravenous medication use processes are developing towards closed-loop medication management systems, combinations of different defenses and their effectiveness in error prevention should be explored. In addition to improved medication safety, implementing new systemic defenses leads to new error types, emphasizing the importance of continuous proactive risk management as an essential part of clinical practice.

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Helsinki, September 2022

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Kuitunen S, Niittynen I, Airaksinen M, Holmström AR. Systemic causes of in-hospital intravenous medication errors: A systematic review. *J Patient Saf* 2021;17(8):e1660-e1668. doi: 10.1097/PTS.0000000000000632 (Open Access)

II Kuitunen SK, Niittynen I, Airaksinen M, Holmström AR. Systemic defenses to prevent intravenous medication errors in hospitals: A systematic review. *J Patient Saf* 2021;17(8):e1669-e1680. doi: 10.1097/PTS.0000000000000688 (Open Access)

III Kuitunen S, Kärkkäinen K, Linden-Lahti C, Schepel L, Holmström A-R. Dose error reduction software in medication safety risk management – Optimising the smart infusion pump dosing limits in neonatal intensive care unit prior to implementation. *BMC Pediatr* 2022;22(1):118. doi: 10.1186/s12887-022-03183-8 (Open Access)

The publications are referred to in the text by their roman numerals (I–III). The original publications are reprinted with the permission of the copyright holders.

DEFINITIONS

Adverse drug event (ADE)
Any injury occurring during the patient's drug therapy resulting from either appropriate care or unsuitable or suboptimal care (1). The definition includes adverse drug reactions (ADRs) and medication errors (MEs).

Adverse drug reaction (ADR)
A response to a medicinal product that is noxious and unintended, resulting not only from the authorized use of a medicinal product at normal doses but also from medication errors and uses outside the terms of the marketing authorization (e.g., off label use), including the misuse and abuse of the medicinal product (EU Directive 2010/84EU).

Cause
An antecedent factor that contributes to an event, effect, result, or outcome (1). A cause may be proximate in that it immediately precedes the outcome, such as an action. A cause may also be remote, such as an underlying structural factor that influences the action, thus contributing to the outcome. Outcomes never have single causes. See also: contributing factor.

Closed-loop medication management system (also closed-loop medication administration/process)
A closed-loop medication management system is a process that ensures correct and adequate recording and transfer of information on the client's/patient's medication by minimizing the risks associated with manual operations and information transfer (2). In a closed-loop medication management system, automation, smart technology solutions, and support systems for decision-making help the healthcare professionals ensure effective, safe, economic, and high-quality healthcare. In the case of the intravenous medication use process, the closed-loop system is reached by integrating electronic health records, barcode medication administration, and smart infusion pumps through interoperability (3,4).

Contributing factor (also contributing hazard)
A circumstance, action, or influence that is thought to have played a part in the origin or development of an incident or to increase the risk of an incident (5). Examples are human factors such as behavior, performance, or communication; system factors such as work environment; and external factors beyond the control of the organization, such as the natural environment or legislative policy. More than one contributing factor and/or hazard is typically involved in a single patient safety incident.

Defense (also systemic defense, barrier, safeguard)
Structures and procedures that are consciously and systematically designed and included in the operational process to identify harmful deviations and prevent them from leading to an incident (6). Some are engineered (e.g., alerts, physical barriers, automatic shutdowns), others rely on people (e.g., surgeons, anesthetists, pilots, control room operators, patients), and yet others depend on procedures and administrative controls (7).

Dose error reduction system/software (DERS)
Refers to the integral computer software in smart infusion pumps intended to aid in the prevention of infusion programming-related errors and warn users of potential over- or under-delivery of a medication or fluid by checking programmed doses/rates against facility-configurable preset limits specific to a medication/fluid and a clinical application (e.g., epidural administration) and/or location (e.g., neonatal intensive care unit, medical/surgical unit) (8).

High-alert medications
Drugs that bear a heightened risk of causing significant patient harm when used in error (9–11). Although mistakes may or may not be more common with these drugs, the consequences of an error are more devastating to patients.

Just culture
Just culture is a key element of safety culture (1). A just culture reconciles professional accountability and the need to create a safe environment to report medication errors; it seeks to balance the need to learn from mistakes and the need to take disciplinary actions. In Just culture, three types of behavioral choices are identified: human error, at-risk behavior, and reckless behavior, the latter of which has zero tolerance (12,13).

Medication error (ME)
Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer (14). Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

Medication safety
Freedom from accidental injury during the course of medication use; activities to avoid, prevent, or correct adverse drug events which may result from the use of medications (1,5).

Medication use process (also medication use system, medication management process/system)
A combination of interdependent processes that share the common goal of safe, effective, appropriate, and efficient provision of medications to patients (1). In a hospital setting, major phases in the medication use process are: planning; selection and procurement; storage; patient admission; ordering, transcribing and reviewing; preparing; dispensing; administration; monitoring; patient discharge; evaluation (15).

Near miss (also close call, good catch, or potential adverse drug event)
An incident that had the potential to cause harm but did not, either by luck or because it was intercepted and corrected before reaching the patient (5,6).

Patient safety
Freedom from accidental injuries during the course of medical care, activities to avoid, prevent, or correct adverse outcomes which may result from the delivery of healthcare (1,5,16).

Neonate
Neonates are the group of children from birth up to and including the age of 27 days, including term and preterm neonates (17).

Risk management
Clinical and administrative activities undertaken to identify, evaluate, and reduce the risk of injury to patients, staff, and visitors and the risk of loss to the organization itself (1). These activities or measures aim to prevent, remedy, or mitigate the occurrence or reoccurrence of an actual or potential (patient) safety event (18). Risk management can be accomplished by both reactive and proactive methods (7,18). Effective risk management means the simultaneous and targeted deployment of limited remedial resources at different system levels (e.g., the individual or team, the task, the situation, and the whole organization) (19).

Safety culture (also a culture of safety)
An integrated pattern of individual and organizational behaviors based upon shared beliefs and values that continuously seeks to minimize patient harm which may result from the processes of care delivery (1).

Smart infusion pump (also smart pump)
An infusion pump with integral computer software (see also: DERS) that is capable of 1) maintaining a drug library of standard drug concentrations, which, when enabled, is used to support dose calculations and alert the user to incorrect orders, calculation errors, or programming errors, that would result in significant over- and under-delivery of a drug or fluid; and 2) capturing

administrative infusion data in a systematic, objective manner to support improvement in safe medication administration (8).

ABBREVIATIONS

ADC	Automated dispensing cabinet
ADE	Adverse drug event
ADR	Adverse drug reaction
BCMA	Barcode medication administration
CDSS	Clinical decision support system
CNS	Central nervous system
CPOE	Computerized prescriber order entry
CVAD	Central venous access device
DERS	Dose error reduction software
D5W	Dextrose 5%
EHR	Electronic health record
ELBW	Extremely low birth weight
eMAR	Electronic medication administration record
ENFit	Medical device connectors for enteral applications
EPS	Enhanced photoemission spectroscopy
FMEA	Failure mode and effects analysis
GA	Gestational age
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HAI	Healthcare-associated infection
HaiPro	Reporting System for Safety Incidents in Health Care Organizations (Finland)
HRHCM	The Joint Commission's High-Reliability Health Care Maturity Model
HRO	High-reliability organization
HUS	Helsinki University Hospital
IA	Intra-arterial
ICU	Intensive care unit
IHI	Institute for Healthcare Improvement's
ISMP	Institute for Safe Medication Practices
ISMP MERP	The ISMP National Medication Error Reporting Program
ISO	International Organization for Standardization
IT	Intrathecal
IV	Intravenous
JCI	Joint Commission International
KCl	Potassium chloride
LASA	Look-alike, sound-alike
LBW	Low birth weight
ME	Medication error
NaCl	Sodium chloride
NCH	New Children's Hospital

NICU	Neonatal intensive care unit
NMB	Neuromuscular blocking agent
NRFit	Medical device connectors for neuraxial applications
NS	Normal saline (NaCl0,9%)
PCA	Patient controlled analgesia
PICC	Peripherally inserted central catheter
PICO	Participants, interventions, comparison, and outcomes
PICU	Pediatric intensive care unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCA	Root cause analysis
RCT	Randomized controlled trial
RFID	Radio frequency identification
SICU	Surgical intensive care unit
SIRS	Systemic inflammatory response syndrome
SOP	Standard operating procedure
VLBW	Very low birth weight
WHO	World Health Organization

1 INTRODUCTION

In recent decades, patient safety has become one of the most important areas of research and development in health systems (1,16,20,21). A significant step forward has been the transition from a "blaming culture" to systems thinking, with the aim of improving the safety of care through risk management based on the identification, analysis and learning from errors and near misses (7,16,19). One of the main threats to patient safety is medication-related incidents, which would often be preventable (21–24). Complex medication use processes, high-alert medications, and high-risk care environments are associated with a more significant risk of errors and serious adverse events (9–11,22,25). High-risk drug treatments are used in hospitals, especially in specialized care settings, intensive care units (ICUs), and emergency departments (23). In addition to the older adults, high-risk patient groups vulnerable to medication errors (MEs) include children, especially neonates (22,25,26).

Intravenous (IV) drug delivery is an example of a high-risk medication use process (27–30). Because of the immediate therapeutic effect and high bioavailability, IV administration routes are widely used in hospitals. IV drugs are associated with the highest ME frequencies and more serious consequences to the patient than any other administration route (27,30,31). For example, the most serious MEs in intensive care are associated with intravenously administered high-alert medications, such as catecholamines, insulin, electrolytes, opioids, and parenteral nutrition (32,33). Consequently, effective interventions to highlight and eliminate errors in the IV drug delivery process are needed (e.g., technology-based solutions and oral syringes that do not fit IV lines) (2–4,8,34,35).

Although medication safety as part of patient safety has been a priority in the Finnish healthcare system during the last decades, the attention paid to IV medication safety remains limited. The research in the hospital setting has focused on other areas, such as overall MEs and adverse drug events (36–38), identification of high-alert medications (39–41) and look-alike sound-alike medications (42), ME reporting systems (43–45), clinical pharmacy services (39,46), automated dispensing systems (47,48), and development of pediatric drug formulations (49,50). The studies related to IV medications mainly focus on drug preparation (51–53) and IV fluids (54). However, in a Finnish study investigating high-alert medications, parenteral drugs were associated with a higher risk for MEs than more frequently used enteral preparations (41).

This study aimed to explore systemic causes of IV MEs and defenses to prevent these errors in a hospital setting to inform preventive risk management actions in healthcare organizations (7,18). The study applied a systems approach to medication risk management based on Reason's (1995,

2000) Theory of Human Error as a theoretical framework (7,19). The literature review describes basic principles of the in-hospital medication use process, emphasizing IV drug delivery. In addition, medication safety of neonatal intensive care unit (NICU) and smart infusion pumps are described as an introduction to the empirical part of the thesis. In the empirical part, research evidence from the scientific literature was first systematically summarized to identify systemic causes of IV MEs (Study I) and systemic defenses to prevent these errors (Study II). After that the development of a dose-error reduction software in a NICU was studied as a systemic defense to prevent IV MEs (Study III). Both qualitative and quantitative research methods were used.

2 REVIEW OF THE LITERATURE

2.1 THEORETICAL FRAMEWORK OF THE STYDY

2.1.1 KEY CONCEPTS OF MEDICATION SAFETY

Safe pharmacotherapy consists of product safety (i.e., drug safety) and process safety (i.e., medication safety) (Figure 1) (6). Medication safety means the safety of the medication use process. It is defined as "a freedom from accidental injury during the course of medication use; activities to avoid, prevent, or correct adverse drug events which may result from the use of medications"(1,5). It focuses on managing medication errors (MEs), which are unintended mistakes in the medication use process caused by omission (not doing something that should have been done) or commission (doing something wrong) (1,6). MEs may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use (14). All MEs can be considered preventable as they are associated with inappropriate drug use (Figure 1) (55). Therefore, their prevention results from improvements in the medication use process. A near miss is an incident that had the potential to cause harm but did not, either by luck or because it was intercepted and corrected before reaching the patient (5,6).

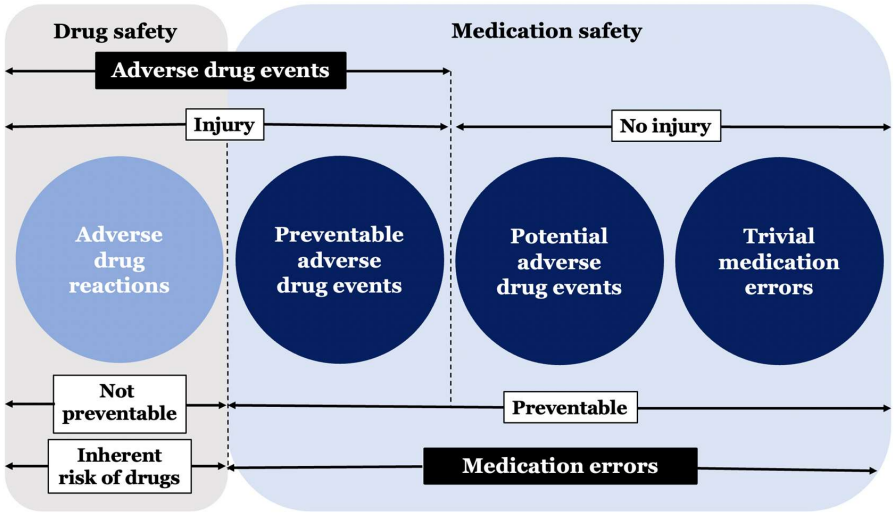

Figure 1. Illustration of the concept safe pharmacotherapy and its division into drug safety and medication safety (6). The figure also shows the relationship between medication errors (MEs), adverse drug reactions (ADRs), and adverse drug events (ADEs). Figure adapted and modified from Otero and Schmitt (2005).

In contrast, drug safety is concentrated on adverse drug reactions (ADRs) (Figure 1). It refers to the safety of drug products and preparations, covering pharmacological properties such as the efficacy and adverse effects of a drug (6). ADRs are potential harm resulting from the drug's intrinsic properties (55). They are monitored closely with pre- and post-marketing pharmacovigilance activities (1,6). An adverse drug event (ADE) is any injury occurring during the patient's medication therapy resulting either from appropriate care or from unsuitable or suboptimal care (1). The definition includes both ADRs and MEs (1,6,55). The relationship and overlap between MEs, ADRs, and ADEs are presented in Figure 1.

In healthcare, risk management is defined as "clinical and administrative activities undertaken to identify, evaluate, and reduce the risk of injury to patients, staff, and visitors and the risk of loss to the organization itself (1)." These activities or measures aim to prevent, remedy, or mitigate the occurrence or reoccurrence of an actual or potential (patient) safety event (18). Risk management can be accomplished by both reactive and proactive methods (7,18).

Reason´s (2000, 1995) Theory of Human Error has been widely used as a theoretical framework in systems-based patient and medication safety work (1,5,7,16,19). The theory is based on observations and research on cultural characteristics of high-reliability organizations (HROs), such as nuclear power plants, aircraft carriers, and air traffic control centers (7). The starting point is that errors are inevitable where there is human action. Systems relying on perfect performance by individuals to prevent errors are doomed to fail for the simple reason that all humans err and frequently (7,19,56). The challenge of human error can be viewed from two perspectives: the person approach and the system approach, which lead to different philosophies of error and risk management (7).

In this study, systems approach was chosen to investigate safety of the IV medication use process in hospital setting. The hospital setting is considered as a HRO with culture of safety to learn from errors and implement systemic defenses for making the care safer (7,16,19,57–59). This has enabled a transition from retrospective error detection towards proactive risk management (7,18,19). In a just culture environment, safety is valued and continuously monitored (1,7,12,13,60). The accountability of errors is divided between the systems and the individuals. Achieving the study objectives requires understanding HROs, systems approach, human error, system accidents, safety culture, and medication risk management.

2.1.2 HIGH-RELIABILITY ORGANIZATIONS (HRO)

Healthcare organizations are often described HROs, which "operate in complex, high-hazard domains for extended periods without serious accidents or catastrophic failures (59)." The concept of high reliability is attractive for health care due to the complexity of systems, processes, and technologies

(7,16,19,57–59). In case of failures, there is a risk of significant and even potentially catastrophic consequences to the patient. Sometimes high reliability is interpreted as effective standardization of health care processes (59). However, the principles of high reliability go beyond standardization; it is better described as a condition of persistent mindfulness within an organization. HROs use systems thinking to evaluate and design for safety continuously (7,19). It is noteworthy that HROs are not immune to adverse events, but they learned to convert these occasional setbacks into enhanced system resilience. As a result, each event is analyzed to effect system-wide change to mitigate the occurrence of similar errors. Errors and failures are seen as high-value opportunities to learn and effect system-wide reform.

At the core of HROs are five key concepts, which are essential for any improvement initiative to succeed (57):

- **Sensitivity to operations**. Preserving constant awareness by leaders and staff of the state of the systems and processes that affect patient care. This awareness is key to noting risks and preventing them.

- **Reluctance to simplify**. Simple processes are good, but simplistic explanations for why things work, or fail are risky. Avoiding overly simple explanations of failure (e.g., unqualified staff, inadequate training, communication failure) is essential to understand the actual reasons patients are placed at risk.

- **Preoccupation with failure**. When near-misses occur, these are viewed as evidence of systems that should be improved to reduce potential harm to patients. Rather than viewing near-misses as proof that the system has effective safeguards, they are viewed as symptomatic of areas needing more attention.

- **Deference to expertize**. If leaders and supervisors are not willing to listen and respond to the insights of staff who know how processes really work and the risks patients really face, you will not have a culture in which high reliability is possible

- **Resilience**. Leaders and staff need to be trained and prepared to respond when system failures occur.

A variety of frameworks and evaluation metrics have been published to support HRO implementation and evaluation (61), such as The Joint Commission's High-Reliability Health Care Maturity Model (HRHCM) (62) and the Institute for Healthcare Improvement's (IHI) Framework for Safe, Reliable and Effective Care (63). The most common implementation strategies of the principles of high-reliability organizations include 1) building and using

data systems to measure progress, 2) developing leadership, 3) supporting a culture of safety, 4) providing training and learning opportunities for providers and staff, and 5) implementing quality improvement interventions to address specific patient safety issues (61–63). Implementing HRO principles, such as a positive organizational culture, have been associated with better patient outcomes (64).

2.1.3 SYSTEMS APPROACH

Human fallibility can be viewed from two perspectives: the person approach or the system approach (Table 1) (7,19). Each perspective has its own idea of error causation and provides different insights into error management. Traditionally, the person approach and blame culture have been dominant perspectives in healthcare. A typical reaction to an accident is focusing on the error and the person involved rather than understanding the systemic cause and contributing factors (7,19,56,65–67). Continued adherence to the person approach is likely to thwart the development of safer healthcare institutions due to the absence of trust and an error reporting culture (7). Establishing learning from errors is one of the key elements of effective risk management. Without a detailed analysis of errors and near misses, the recurrence of similar incidents cannot be prevented. Another serious weakness of the person approach is that focusing on the individual origins of error isolates unsafe acts from their system context. As a result, two important features of human error tend to be overlooked: it is often the best people who make the worst mistakes, and mishaps tend to fall into recurrent patterns (7,19,56,67). The same set of circumstances can provoke similar errors, regardless of the people involved.

A systems approach should be undertaken at institutions to change working conditions and build systemic defenses, barriers, and safeguards to prevent errors from occurring or mitigate the harm if errors do occur (Table 1) (7,15,19,56,65,67,68). The systems approach states that errors result from the conditions under which the individuals work (Table 1) (7,19,68). Hence, errors may be viewed as consequences of systematic failures and organizational weaknesses. System defenses are built to support the correct and secure execution of the process. However, correcting systems failures will not eliminate all errors because individuals still bring various abilities and work habits to the workplace (56). Nonetheless, system redesign will substantially reduce the probability of error.

Table 1. *The differences between the person and the system approaches to human error and examples of applying these to medication safety incidents* (7,67). *CDSS=clinical decision support system; CPOE=computerized prescriber order entry; LASA=look-alike, sound-alike; KCl=potassium chloride; NS=Normal saline (NaCl0,9%).*

	Personal approach	System approach
Focus	Unsafe acts (e.g., errors and procedural violations) of individuals. Blaming individuals for making errors.	Errors in conditions under which individuals work: how and why the defenses failed? Development of error prevention strategies. Tendency towards proactive risk management.
Premise	"Errors happen to non-competent professionals." "Bad things happen to bad people."	"Humans make mistakes, and errors occur even in high-quality organizations and to the most competent workers."
Causes of errors	Mental processes (e.g., forgetfulness, inattention, poor motivation, carelessness, negligence, and recklessness.	Systemic factors, such as weaknesses in complex organizational processes and unclear responsibilities.
Countermeasures	Attempts to change human behavior (e.g., writing or updating a procedure, disciplinary measures, the threat of litigation, retraining, naming, blaming, shaming).	Attempts to change working conditions by building systemic defenses and safeguards to reduce and prevent errors, learning from errors.
Effectiveness	Similar errors may still occur under similar conditions.	The recurrence of similar errors is prevented by building systemic defenses and safeguards.
Example 1. Actions to ensure correct orders and prevent prescribing errors in a ward using the CPOE system.	A CPOE system without instant feedback of an error to a prescriber, blaming the physician who made the error, and education to assure that physicians remember how to order medications correctly.	Seeking to design systems that make it harder to err and make errors that do happen more visible to initiate corrective actions (e.g., implementation of CDSS alerts and forcing functions to CPOE inform the prescriber of out-of-range doses to correct the error before it reaches the patient).
Example 2. Actions to ensure safe storage of high-alert drugs to prevent mix-ups between LASA-drugs (e.g., ampoules of KCl concentrate and NS).	Keeping KCl in the same storage with all other drugs and concentrations, educating the staff to pay more attention to look-alike vials, adding warning labels or signs, and making the labels on the medications appear more distinct.	Eliminating the opportunity for error to occur by redesigning the system of drug storage and access (e.g., removing KCl concentrate to a separate, perhaps locked, storage area to eliminate the possibility of error).

2.1.4 HUMAN ERROR

According to Reason's theory (1995, 2000), an error is the failure of planned actions to achieve their desired goal (7,19). Errors can be further classified into two categories: slips or lapses versus mistakes (Figure 2) (7,19,68). In case of slips and lapses, the plan is adequate, but the associated actions do not go as intended. The error usually occurs in familiar surroundings during the largely automatic performance of a routine task. Slips relate to observable actions and are associated with attentional failures (e.g., recognition failures and selection failures). Lapses are more internal events and relate to failures of memory and attention. On the contrary, in case of mistakes, the actions may go entirely as planned, but the plan is inadequate to achieve its intended outcome. The failure lies at a higher level: the mental processes involved in planning, formulating intentions, judging, and problem-solving. Mistakes can be further classified into rule-based mistakes and knowledge-based mistakes.

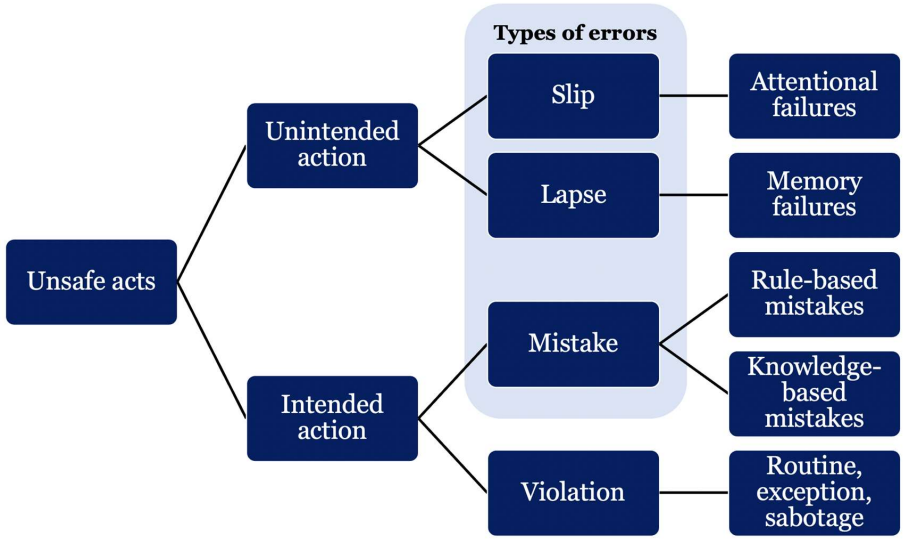

Figure 2. Taxonomy of unsafe acts, distinguishing between voluntary and involuntary actions and the cognitive function involved (execution, memorization, planning) (adapted from 7,19).

It is important to distinguish errors from deliberate violations (Figure 2) (7,19). Violations are defined as "deviations from safe operating practices, procedures, standards, or rules." They fall into three main groups: routine violations entailing cutting corners whenever possible, optimizing violations taken to further personal rather than task-related goals, and necessary or situational violations that seem to offer the only possible way to getting the job done, and where the rules or procedures seem to be inappropriate for the

present situation. Errors arise mainly from problems related to information (e.g., forgetting, inattention, lack of knowledge), which is why they can be reduced by improving the information flow within the workplace. Unlike these examples, violations are associated with motivational problems and require motivational and organizational remedies.

People can contribute to the accident in two different ways depending on the length of time that passes before human failures are shown to have an adverse impact on safety (Figure 3) (7,19,68). Active failures are unsafe acts with immediate consequences, such as errors and violations committed by those "at the sharp-end" of the system (e.g., nurses, physicians, pharmacists). Examples of active failures include slips, memory lapses, rule violations, and confirmation bias. On the contrary, latent failures are created because of decisions made at the higher levels of an organization (e.g., management decisions, selecting look-alike medication vials to the hospital's formulary, inadequate or questionable policies). The damaging consequences of these contributing factors may lie dormant within the system for many years before they combine with active failures and local triggers to create an accident opportunity. Unlike active failures, whose specific forms are often hard to foresee, latent conditions can be identified and remedied before an adverse event occurs. Understanding this background leads to proactive rather than reactive risk management.

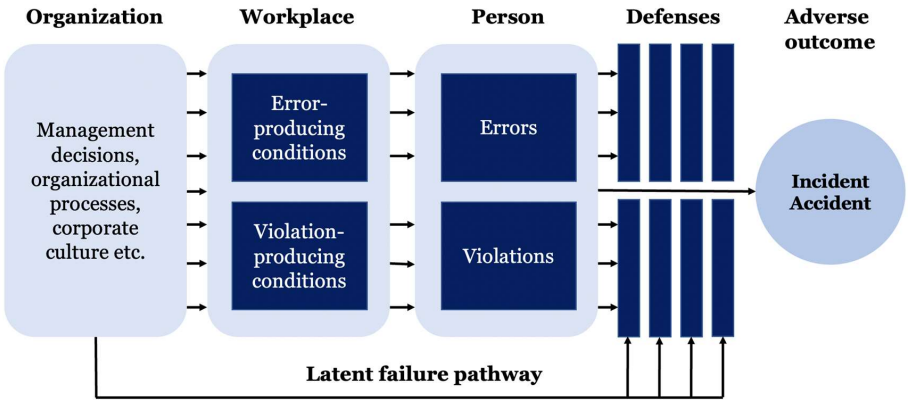

Figure 3. The stages in the development of an organizational accident (adapted from 19,68). Active failures (i.e., errors and violations) are unsafe acts committed by the people "at the sharp-end." Latent failures are created because of decisions made at the higher levels of an organization. In the case of active failures, the negative outcome is almost immediate. However, the consequences of human actions or decisions can take a long time to be disclosed for latent conditions.

2.1.5 THE "SWISS CHEESE MODEL" OF SYSTEM ACCIDENTS

Reason (2000) has visualized system accidents by utilizing the "Swiss cheese model," which has been widely used to analyze medication errors (Figure 4)

(7). The slices of cheese present the protective systemic defenses and the holes systemic failures (i.e., active failures and latent conditions). In an ideal world, each defensive layer would be intact. However, they are more like slices of Swiss cheese with many holes, continually opening, shutting, and shifting their location. The presence of holes in one slice does not typically cause a bad outcome, but when the holes in many layers momentarily line up, it creates an opportunity for an accident. This case illustrates how analyses of catastrophic systems failures reveal multiple, often latent failures leading up to the actual hazard. In health care, many of the slices of cheese already have their holes aligned, so one slice of cheese may be all that is left between the patient and the significant hazard.

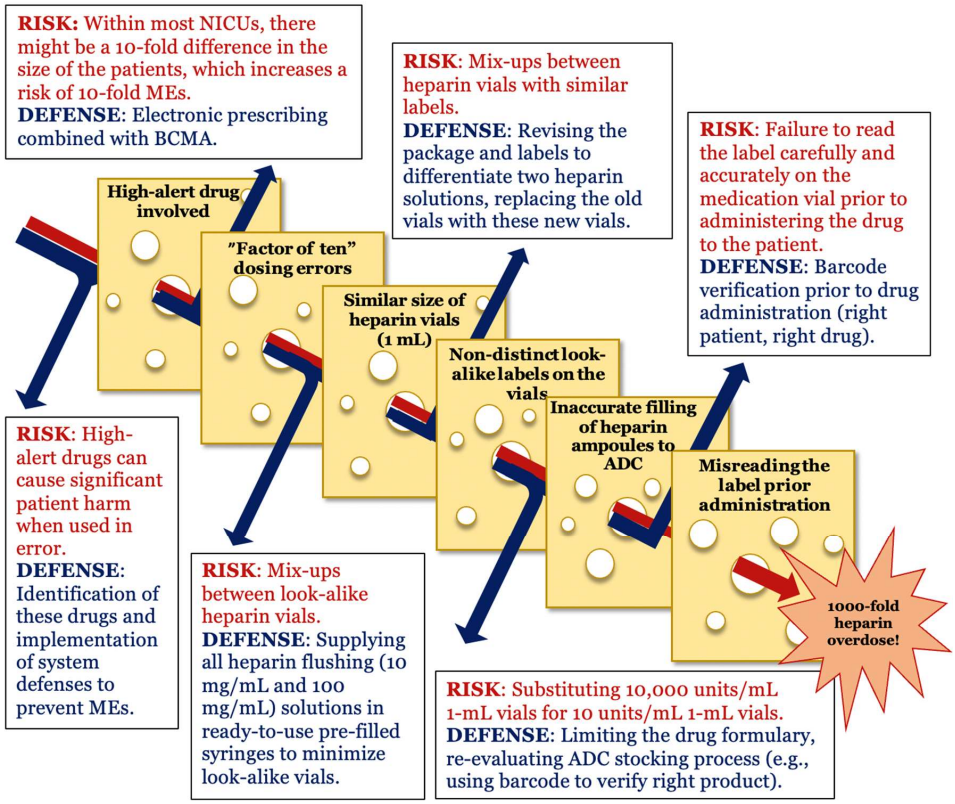

Figure 4. Application of Reason's (2000) "Swiss cheese model" to a medication error (ME), which led to a potentially fatal heparin overdose in a neonatal intensive care unit (NICU) (adapted from 7,69). The presented case is a synthesis of nine MEs where neonates were inadvertently administered a 1000-fold higher heparin dose than what was intended as a line flush. All these MEs were associated with several simultaneous failures in the medication use process. ADC=automated dispensing cabinet, BCMA=barcode medication administration.

2.1.6 SAFETY CULTURE AND JUST CULTURE

Applying systems approach to medication safety risk management requires an established safety culture within the organization (1,7,15,16,24). Safety culture is defined as "an integrated pattern of individual and organizational behavior based upon shared beliefs and values, that continuously seeks to minimize patient harm which may result from the processes of care delivery (1)."

Traditionally, blame culture has dominated in hierarchical healthcare organizations, and mistakes remain silent or discussed behind closed doors (7,16,56,60). The development toward a blame-free healthcare culture has been crucial to increasing the transparency and ability of healthcare organizations, for example, to report and deal with MEs for learning purposes. However, a blame-free culture fails to confront individuals who willfully and repeatedly make unsafe behavioral choices in clinical practice (12,13,70).

Finding a balance between punishment and blamelessness is the basis for developing a just culture, where safety accountability is divided between the systems and the individuals (1,7,12,13). A just culture reconciles professional accountability and the need to create a safe environment to report MEs; it seeks to balance the need to learn from mistakes and to take disciplinary actions (1). Three types of behavioral choices are identified: human error, at-risk behavior, and reckless behavior (Table 2) (12,13). Each type of behavior has a different cause, and consequently, a different response is required.

When errors happen, it is important to identify and solve both behavioral choices, especially reckless behavior (active failures), and the issues related to system design (latent failures) (Table 2) (12,13). The core idea is that good system design, and good behavioral choices of staff together produce good outcomes. A learning culture is more likely to occur in organizations that elicit greater employee involvement in decision making, which is why human resource management capabilities play an important role in moving from a blame culture to a just culture (60).

A just culture environment should also include a support system for second victims (15,71). A second victim is a health care provider involved in an unanticipated adverse patient event, medical error, and/or a patient-related injury who becomes victimized in the sense that the provider is traumatized by the event (72). Frequently, second victims feel personally responsible for the unexpected patient outcomes and feel they have failed their patients, second-guessing their clinical skills and knowledge base.

Table 2. *The differences between human error, at-risk behavior, and reckless behavior* (7,12,13). *ADC=automated dispensing cabinet.*

	Human error	At-risk behavior	Reckless behavior
Definition	Inevitable, unpredictable, and unintentional failure (e.g., a slip, lapse, or mistake).	A choice made by the individual when the risk was mistakenly believed to be insignificant or justified.	Conscious disregard of a substantial and unjustifiable risk, of which the individual is aware.
Examples	Mistakes can be skill-based (e.g., omissions), rule-based (e.g., using a new infusion pump incorrectly like the older model), or knowledge-based (e.g., a drug overdose due to a knowledge deficit about a patient's recent weight loss).	Using shortcuts to manage system problems and time urgency (e.g., bypassing drug interaction alerts, scanning the barcode on the first container several times when multiple containers are used for an admixture, drug storage outside an ADC).	Behavior that endangers the safety of other people (e.g., drug diversion, retaliatory breaches in patient confidentiality, performing surgery under the influence of drugs or alcohol).
Causes	Endogenous 'random human errors' arise within an individual from a random and unpredictable cognitive event. In exogenous "system-based human errors," some environment features contribute to a failure in cognitive processes.	System failures make it difficult or impossible to execute tasks as designed can lead to taking short-cuts and breaching procedures (e.g., patient's drug is missing on the unit, access to the ADC is crowded and time-consuming, the new barcode scanner with a high rate of scanning failures).	The reasons for engaging in reckless behavior are varied. Most often, the person making a reckless choice is motivated by a self-centered desire to put their own needs ahead of others.
Management	The redesign makes the system human error-proof or error-resistant (e.g., standardization and simplification, barriers, forcing functions, automation, and technology). Discipline and counseling are not warranted or effective.	Admitting that at-risk behavior exists, removing the system barriers to safe behavioral choices, removing the rewards for at-risk behaviors, and coaching individuals to see the risk associated with their choices.	Reckless behavior is blameworthy behavior. Swift and appropriate remedial or disciplinary actions should be considered. System redesign to protect against future reckless behavior.

2.1.7 MEDICATION RISK MANAGEMENT IN HOSPITALS

In a just culture environment, safety is valued, reporting and open discussion of safety risks is encouraged without penalization, and people throughout all organizational levels are held accountable using a clear and transparent process that evaluates the errors (7,12,13). System resilience includes reactive and proactive risk-management strategies (Table 3) (7,18). It is defined as the degree to which a system continuously prevents, detects, mitigates, or ameliorates hazards or incidents so that an organization can bounce back to its original ability to provide core functions.

Table 3. *Examples of reactive and proactive methods to identify and analyze MEs to redesign medication use processes safer in hospitals* (15,18,56). *FMEA=failure mode and effects analysis, ME=medication error, RCA=root cause analysis.*

Reactive methods	Proactive methods
• ME reporting system • Analyzing ME reports (e.g., RCA) • Trigger tools • Chart review • Data from technology • Direct observation • Medication-use evaluation • A multidisciplinary team analyzing identified medication safety issues	• Medication safety self-assessment • Other risk-assessment tools (e.g., guidelines, best practices) • Medication safety risks reported in the literature and other organizations • FMEA and gap assessment • A multidisciplinary team identifying safety issues and implementing systemic defenses proactively

An interdisciplinary medication safety team approach is recommended in hospitals to retrospectively analyze the identified medication safety issues and problems and proactively assess risk (Table 3) (15). To ensure overall success, a medication safety officer, preferably a pharmacist, should lead the medication safety efforts throughout the organization (73,74). Other crucial areas include elements in place to provide the structure for safe medication practices, a successful strategic plan, and continuous improvement philosophy (15,73,74).

Traditionally risk management in healthcare organizations has been based on retrospective and reactive methods, which means learning from previous incidents to minimize similar errors in the future (Table 3). Therefore, an essential component of risk management is a system for reporting and reviewing MEs and near-misses (15,16,24,43,45,56,75). Also, in Finland, analyzing ME reports for learning purposes has been fundamental for understanding medication use processes and related safety risks in various health care settings (36–39,43). This has resulted in implementation of proactive systemic defenses and safer practices related to prescribing,

preparation, and administration of drugs, use processes of high-alert medications, and medication reconciliation and reviews (39,46,76).

Despite the development of medication use processes, ME reporting is still needed to supplement systemic defenses by providing important signals about high-risk situations, medications, and patient groups (15,16,24,43,45,56,75). A similar need has also been identified on the pharmacovigilance side, where detection of risk signals still plays an important role (77). However, underreporting MEs is a widely known problem, and it has been noted that healthcare providers prioritize situational problem-solving instead of reporting in situations that can be resolved (78,79). For example, handling near misses is often seen as unworthy of reporting since it does not result in actual harm. Therefore, it is important to complement error-reporting efforts by using other retrospective safety event detection methods and try to shift towards proactive risk management (Table 3).

The idea of proactive risk-management activities is to prevent harmful MEs before they happen (Table 3) (7,15,18,56). As an example, Institute for Safe Medication Practices (ISMP) has published self-assessment tools, such as to assess medication safety in hospitals (80) and safe handling of high alert medications (81). In addition, ISMP has generated several guidelines related to specific areas on medication safety, such as adult IV push medications (82), implementation of smart infusion pumps (8), safe preparation of compounded sterile preparations (35), and safe use of automated dispensing cabinets (83). In Finland, a medication safety self-assessment tool for hospital wards has been developed by adapting ISMP's Medication Safety Self-Assessment tool for hospitals (84), and it has been recently updated (85). A failure mode and effects analysis (FMEA) can be used to evaluate risks related to a new system, process, or equipment prior to implementation, as it enables the monitoring of changes (15,18).

Restructuring the medication use process and building up new systemic defenses or strengthening existing ones is as important as risk identification. The purpose of risk-reduction strategies can either prevent errors, make errors visible, or mitigate the harm if an error occurs (Table 4) (7,15,86,87). Effective and successful systemic defenses will address the underlying cause of error and impact as many steps of the medication use process as possible, as more than one risk-reduction strategy is needed in many cases. The most powerful error-reduction strategies focus on changes to the system in which individuals operate, following with strategies that target system changes, but rely in some part on human vigilance and memory (Table 4) (87). However, the most familiar and often easy-to-implement steps rely entirely on human vigilance, which reduces their effectiveness in error-prevention.

Table 4. *Examples of error-reduction strategies to create system changes for safe medication use. The strategies are presented in order of effectiveness in error prevention with examples of practical applications* (adapted from 87). *ADC=automated dispensing cabinet, CPOE=computerized prescriber order entry, CDSS=clinical decision support system, IV=intravenous, LASA=look alike, sound alike.*

Error-reduction strategy	Power
Fail-safes and constraints involve actual system changes in the design of products or how individuals interact within the system (e.g., using fingerprint verification to enter ADC).	**High**
Forcing functions are procedures that create a "hard stop" during a process to help ensure that important information is provided before proceeding (e.g., hard limits in smart pumps).	
Automation and computerization of medication use processes and tasks can lessen human fallibility by limiting reliance on memory (e.g., using CPOE with CDSS in prescribing).	
Standardization creates a uniform model in performing various functions, and it tends to reduce the complexity and variation (e.g., standard concentrations if IV infusions).	
Redundancies incorporate duplicate steps or add another individual to a process to force additional checks in the system (e.g., order verification and independent double-checks).	
Reminders and checklists help make important information readily available (e.g., using auxiliary labels to distinguish LASA-drugs).	
Rules and policies are useful and necessary in organizations, and when effective, they should guide staff toward an intended positive outcome.	
When combined with other strategies that strengthen the medication-use system, **education and information** are important tactics.	
Suggestions to be more careful or vigilant.	**Low**

It is recommended to utilize literature to identify both medication safety risks and risk-reduction strategies that have been proven effective, recommended by experts, or implemented successfully elsewhere (15,88). Healthcare organizations are widely adopting new technologies, which should be carefully evaluated before implementation from the medication safety point of view (15,86). It is important to be aware that introducing a new system or even smaller changes in the workflow can cause new unpredictable risks (19). However, the original purpose was specifically to prevent errors. Therefore, the effectiveness, adequacy, and utilization rate of systemic defenses should be continuously monitored and re-evaluated (15).

2.2 HIGH-RISK SITUATIONS IN HOSPITAL SETTING

Hospitals are often regarded as high-risk settings in terms of associated risk for MEs during the care. The key areas of WHO's third Global Patient Safety Challenge "Medication without harm," are high-risk situations, polypharmacy, and care transitions. High-risk situations include high-risk settings, high-risk patients, and high-alert medications (Figure 5) (22,25). MEs are often caused by a combination of medication, provider and patient, and systems factors; therefore, a range of sustainable strategies of proven efficacy should be developed and implemented in conjunction. The high-risk situations from the perspective of this study are presented in Figure 5. The key medication safety risks related to IV administration route, high-alert medications, and medication use process in NICU settings are reviewed in more detail in the following sections.

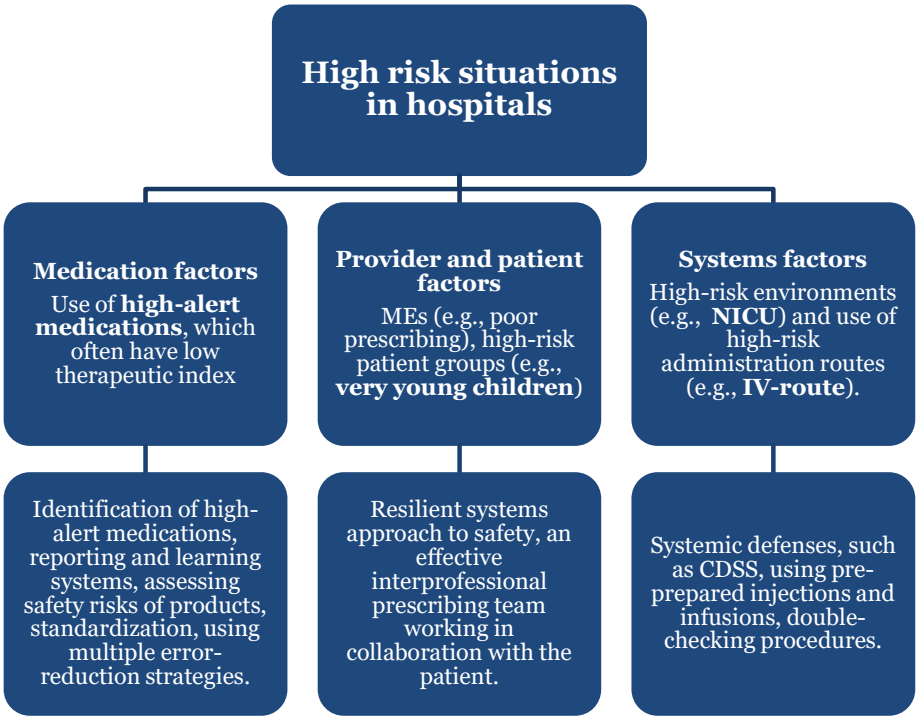

Figure 5. Examples of common high-risk situations related to medication safety in hospital settings (22,25). CDSS=clinical decision support system, IV=intravenous, ME=medication error, NICU=neonatal intensive care unit.

2.2.1 INTRAVENOUS MEDICATION ADMINISTRATION AS A HIGH-RISK ADMINISTRATION ROUTE

2.2.1.1 Basic principles of intravenous medication administration

Intravenous (IV) drug delivery is a complex process involving multiple possibilities for error (28,89–94). The bioavailability of IV-administered medication is high, the therapeutic dose range is often narrow, and effects are hard to undo (95,96). The drugs may be either injected all at once or infused slowly through a vein into the plasma at a constant rate (Table 5). Administration of the medication by continuous IV infusion allows the precise control of plasma drug concentrations to fit the patient's individual needs, especially for drugs with a narrow therapeutic window (e.g., heparin) (Table 5) (96). An effective constant plasma drug concentration is maintained by eliminating wide fluctuations between the maximum and minimum plasma concentrations. The duration of drug therapy may be maintained or terminated as needed. Slow IV infusion may be used to avoid adverse effects due to rapid drug administration. (E.g., fast IV infusion of human immunoglobulin may cause a rapid fall in blood pressure and possible anaphylactic shock. Or a rapid IV push of antiarrhythmics may cause an adverse response due to the initial high drug plasma concentrations before slow equilibration with the tissues). To avoid complications, the IV route should be treated appropriately between the administration of different drugs and when no drugs are administered (Table 5).

IV administration routes are widely used in high-risk hospital settings, such as ICUs, perioperative care, and emergency departments because of the immediate therapeutic effect and high bioavailability. In addition to inpatient hospital care, IV administration is used to treat patients in ambulatory settings (e.g., administering chemotherapy, biological drugs, palliative care, and antimicrobials in a day hospital or at home) (97). IV medications can be administered to either a peripheral or central route, depending on the patient's condition, total medication regimen, and expected duration of drug treatment (98,99). It has been estimated that more than half of hospitalized patients have a peripheral catheter in place (100). Short peripheral catheters are widely used for time-limited IV infusion therapy, IV bolus drug administration, and phlebotomy for blood sampling (99). They are not suitable to administer IV solutions with high osmolarity or viscosity, vesicant, or irritating medications, drugs or fluids with high infusion rates, or long-term (>1 week) IV infusion therapy. Midline catheters are inserted in the upper arm or antecubital area, enabling more concentrated solutions to be infused. They may remain in place longer than short peripheral catheters.

Table 5. *Different types of intravenously administered drug doses (8,95,96). CVAD=central venous access device, D5W=dextrose 5%, IV=intravenous, KCl=potassium chloride, NaCl=sodium chloride, NMB=neuromuscular blocking agent, NS=normal saline (0.9% sodium chloride).*

Type	Definition	Examples of intended use
IV push or bolus	Direct manual administration of medication using a syringe, usually under pressure, connected to an IV access device; these cases may include a manually administered IV bolus dose in an emergency.	• An immediate drug effect and high concentration is necessary (e.g., NMBs, sedation, and opioids during intubation) • Patient receiving multiple IV drugs with fluid restrictions or a limited number of IV routes available (e.g., antibiotics)
Intermittent infusion	A medication or fluid infusion is delivered over a specified time at prescribed intervals.	• Medications with a long half-life, administered as a regular course, and not critical for vital functions (e.g., antibiotics, biological drugs, chemotherapy)
Loading dose infusion	The initial dose of a medication given by infusion is intended to rapidly achieve a therapeutic level prior to initiating the continuous or scheduled maintenance dose infusion.	• Initiation of a continuous vasoactive infusion (e.g., epinephrine) • Initiation of intermittent phosphenytoin IV infusions to treat status epilepticus
Continuous infusion	A medication or fluid prescribed with a dose rate (e.g., 10 mg/kg/min) or infusion rate (e.g., mL/hour) may change during the infusion. The infusion continues until therapy is no longer required or when the solution container is depleted.	• A sedative IV infusion (e.g., dexmedetomidine, midazolam) • Parenteral nutrition or continuous IV fluid (e.g., D5W with KCl and NaCl additives)
Flush or flushing	Administration of a compatible IV fluid through an IV line so that the existing contents of the line are flushed into the patient's bloodstream. This method ensures that fluid residual IV drug of fluid in the dead volume has been administered or cleared from the IV line.	• Using a prefilled NS syringe to flush an infusion line after an IV injection manually • Administering NS via infusion pump (or D5W if NS not compatible, e.g., amiodarone) after an IV infusion
Locking	The instillation of a solution into a vascular access device is used to maintain patency between use and/or reduce the risk of catheter-associated bloodstream infection.	• Using NS or heparin to lock each CVAD lumen after final flushing to decrease the risk of intraluminal occlusion

A central venous access device (CVAD) is indicated when the peripheral route is unavailable or not recommended. (E.g., trauma patients with massive fluid replacements, surgical patients requiring rapid administration of IV fluids, and patients with poor peripheral veins, multiple, incompatible IV drugs, or IV infusions irritating or damaging peripheral veins) (98). Nontunneled CVADs are recommended for short-term use (from days to weeks), peripherally inserted central catheters (PICCs) for short- to medium-term use (from weeks to months), and tunneled CVADs for long-term use (months to years). The goal for all CVADs is to provide safe and reliable vascular access without complications related to insertion, maintenance, or removal. In addition to hospitals, CVAD can be used in home care, ambulatory care clinics, or infusion centers for patients who require administration of continuous or intermittent infusions over a long period of time (e.g., chemotherapy, parenteral nutrition). Because the CVAD tip rests in an area with a rapid flow of a large amount of blood and the infusion is diluted immediately, administration of large volumes of fluids in a short period of time, vesicant or irritating drugs (e.g., antineoplastic medication, vasopressors), or highly concentrated solutions with an osmolarity >600 mOsm/L or a pH <5 or >9 (e.g., parenteral nutrition) is possible. CVADs may have several lumens permitting concurrent administration of incompatible IV medications simultaneously.

2.2.1.2 Complications associated with intravenous drug administration

Examples of possible complications related to IV drugs and vascular access devices are presented in Table 6. Peripheral catheters and CVADs are associated with infections, occlusion, catheter-associated deep vein thrombosis, infiltration, extravasation, phlebitis, catheter damage, dislodgement, and malposition (101,102). In addition to IV administration and catheter handling, microbial contamination can also occur while reconstituting an IV drug (e.g., environmental contamination, poor technique, using multidose vials) (51–53,103). Ensuring compatibility of all ingredients before IV dose compounding or administration of two drugs simultaneously to the same infusion line through a Y-site connector is important because precipitation may induce organ failure, particular pulmonary toxicity, and systemic inflammatory response syndrome (SIRS) (104,105). In addition, it is crucial to prevent other particles (e.g., glass from ampoules, if filter needles are not used) or air from entering the infusion system (103).

Table 6. *A synthesis of complications associated with intravenous drugs and vascular administration systems* (51–53,101–105). *CVAD=central venous access device.*

Complication	Definition
Air embolism	The presence of air in the vascular system obstructs blood flow primarily to the lungs or brain.
Anaphylaxis	A severe, potentially life-threatening allergic reaction with immunologic and nonimmunologic causes.
Catheter-associated deep vein thrombosis	Thrombosis (blood clot) formation is associated with the presence of a vascular access device.
Catheter dislodgement	Catheter movement into or out of the insertion site indicating tip movement to a suboptimal position; may be partial or total.
CVAD malposition	CVAD tip located in an aberrant position and no longer located in the original vena cava or cavoatrial junction, which can occur during the insertion procedure or at any time during the catheter use.
Extravasation	The inadvertent infiltration of vesicant solution or drug (e.g., chemotherapy) into the surrounding tissue.
Incompatibility	Drugs or fluids incapable of being mixed or used simultaneously without undergoing chemical or physical changes or producing undesirable effects.
Catheter-associated bloodstream infection	An infection occurring from 4 possible sources: 1) During catheter insertion/during catheter dwell time through migration of microbes down the catheter tract. 2) Via the catheter hub/lumen during routine administration and manipulation at the hub/lumen. 3) Due to endogenous microorganisms within the bloodstream. 4) From contaminated infusates.
Infiltration	Inadvertent administration of a nonvesicant solution or medication into surrounding tissue.
Occlusion	Obstruction of a vascular access device lumen, preventing or limiting the ability to flush and/or administer solutions through a lumen or withdraw blood.
Phlebitis	Inflammation of a vein; may be accompanied by pain/tenderness, erythema, edema, purulence, and/or palpable venous cord.

2.2.1.3 Intravenous medication errors

IV drugs are associated with the highest ME frequencies and more serious consequences to the patient than any other administration route (27,29–31,106). Examples of life-threatening MEs involving the IV administration route are presented in Table 7. A meta-analysis of observational studies from the United Kingdom demonstrated that administration errors are as much as five times more likely when an IV route is used (29). It has been estimated that approximately 10% of IV medication administrations include an error (91). In a study exploring MEs and ADEs of pediatric inpatients, IV medications were associated with 54% of potential ADEs (106). Recent observational multisite studies conducted in the United States and the United Kingdom have reported a high prevalence of IV infusion administration errors and procedural failures, even with the use of smart infusion pumps (93,94).

Studies have found administration and preparation errors the most common IV ME types, as these phases of the medication use process are the most widely studied (28,89,91). According to a systematic review exploring intravenous MEs in the United Kingdom, most (32%) of IV MEs were administration errors, and 9% of errors occurred during preparation (91). The only studies presenting data for prescribing errors were those using spontaneous reporting methods associated with underreporting, which is why the incidence of prescribing errors appeared to be very low (<1%). The number of IV prescribing errors is likely to be higher. Overall, prescribing and monitoring stages of the medication use process have been identified as the source of the highest prevalence rates of preventable medication harm (23). Wrong administration rate errors have been identified as the most common error type in IV drug administration (mean incidence rate 58%). This error is followed by the wrong time of administration (20%) and the remaining error types (wrong dose, wrong diluent, wrong volume, wrong pump setting, and dose omission (91). A systematic review exploring IV preparation errors compared incidence by preparation site and/or method, finding that error incidence to be lower for doses prepared within a central pharmacy versus the nursing ward and lower for automated preparation versus manual preparation (89). The same systematic review also found out that error types and reported rates varied substantially, including wrong drug (0–5%), wrong diluent solution (0–49%), wrong label (0–99%), wrong dose (0%–33%), wrong concentration (0%–89%), wrong diluent volume (0–49%) and inadequate aseptic technique (0–93%).

Table 7. *A synthesis of life-threatening intravenous (IV) medication errors (MEs), error consequences, and safety recommendations identified in the literature* (8,16,34,35,82,88,107–116). *ADR=adverse drug reaction, CNS=central nervous system, DERS=dose error reduction system, D5W=dextrose 5%, ENFit=medical device connectors for enteral applications, HAI=healthcare-associated infection, ISO=International Organization for Standardization, IT=intrathecal, KCl=potassium chloride, NMBs=neuromuscular blocking agents, NRFit=medical device connectors for neuraxial applications, NS=normal saline (0.9% sodium chloride).*

Risk	Examples of MEs and error consequences	Recommendations
Accidental administration of NMBs to patients without ventilator assistance	Wrong drug errors lead to inadvertent administration of NMBs to both adult and pediatric patients. Consequences: serious, permanent injuries or event death due to paralysis of respiratory muscles.	Segregating, sequestering, and differentiating all NMBs from other medications, wherever they are stored in the organization.
Accidental administration of an IV infusion of sterile water to a patient	Mix-ups between similar-looking 1 L bags of sterile water with 1 L bags of D5W or NS. Consequences: hemolysis resulting in patient harm and even death.	Eliminating all 1,000 mL bags of sterile water (labeled for "injection," "irrigation," or "inhalation") from all areas outside of the pharmacy.
Delayed administration of antidote, reversal agent, or rescue agent in case of ME or ADR	Delay in administering the appropriate antidote, reversal agent, or rescue agent (e.g., EPINEPHrine for anaphylaxis). Consequences: serious harm or even death.	Ensuring readily available, standardized protocols and/or coupled order sets in place that permit the emergency administration, directions for use, and administration.
Drawing more than one dose into a syringe in anticipation of needing additional doses	E.g. 100 mg ketamine ordered, the total volume of 5 mL (500 mg) drawn into a syringe from 100 mg/mL vial. Consequences: death after an inadvertent administration of the whole syringe.	Wherever possible, prefilled pharmacy-prepared or commercially available syringes that contain the exact dose should be used.
Failure to disinfect ports and use sterile caps	Failing to place a sterile cap on the end of a reusable IV administration set left hanging between use and/or to properly disinfect the port when accessing needleless valves on an IV set. Consequences: contamination of sterile equipment and risk of an HAI.	The development of procedures incorporating manufacturer-recommended disinfection protocols for their needleless connectors and placing a sterile cap on the end of the IV tubing between intermittent infusions.
Inadvertent arterial injection or IV extravasation	Inadvertent arterial injection or IV extravasation of injectable promethazine. Consequences: serious tissue injuries and amputations.	Eliminating injectable promethazine from the formulary.

Inadvertent administration of concentrated electrolytes (e.g., KCl, NaCl) undiluted	Confusing KCl ampoule with another injectable drug during injection preparation or misinterpretation of a verbal order (preparation of IV injection instead of infusion). Consequences: a patient death.	Replacing concentrated KCl solutions in patient care units with appropriate KCl dilutions compounded in the pharmacy. KCl is never intentionally used undiluted, so there is no need to stock the concentrate on the care units.
Infusion pump programming errors	Administration of high-dose fluorouracil IV infusion over 4 hours instead of 4 days via ambulatory infusion pump. Consequences: profound mucositis, pancytopenia, hemodynamic collapse, and multiorgan failure resulting in patient death.	Infusion pumps with DERS, ≥ 95% DERS compliance, protocols for accidental overdoses, standardizing key information on pharmacy labels, independent double-check.
MEs during sterile compounding of drugs	Preparation of the wrong concentration/strength or using the wrong product/diluent. Consequences: serious errors are causing patient harm or death.	An independent double-check of drugs and diluents. This process includes confirmation of the proper volume of each ingredient prior to its addition to the final container. Using commercially available IV solutions or preparation in the pharmacy, rather than preparation by nurses on patient care units.
Unnecessary dilution of IV push medications	Dilution of prefilled syringes to avoid discomfort or extravasation of vesicants or help slow injection. Consequences: errors, contamination, and infection.	Reducing unnecessary dilution and/or providing the products in different forms/strengths so nurses do not feel they must dilute them.
Unintended IV administration of epidural medications	Administration of epidural bupivacaine infusion IV due to similar-looking tubing. Consequences: cardiotoxicity (e.g., profound disturbances in cardiac rhythm and contractility resistant to typical resuscitation efforts).	NRFit connectors, syringes, and administration sets meet the ISO 80369-6 standard for neuraxial drugs. Labeling: "FOR EPIDURAL USE ONLY," clearly defined administration route in all orders, storing and dispensing epidural and IV drugs separately, using separated pumps designated to epidural infusions.
Unintended IT administration of IV medications	Administration of IV vincristine mistakenly IT instead of another syringe supposed to be given IT to the same leukemic patient (e.g., methotrexate). Consequences: CNS destruction, fatal neurological symptoms.	Dispense vincristine and other IV vinca alkaloids in a minibag of a compatible solution and not in a syringe.
Unintended IV administration of oral liquid medications	Administration of enteral feeding IV due to similar-looking syringes. Consequences: death of an infant.	Tubing and connectors meet the ISO 80369-1 standard for oral or enteral drug administration using ENFit syringes.

2.2.1.4 Intravenous medication use process in Helsinki University Hospital (HUS)

New systemic defenses to ensure safe IV medication use process have been implemented recently in inpatient wards and intensive care units (ICUs) in Helsinki University Hospital (HUS) when the new electronic health record (EHR) system Apotti was introduced in multiple phases during 2018–2020 (Figure 6) (117). Efforts have been made to improve medication safety by introducing some features of closed-loop medication management systems which have not been implemented in Finnish hospitals before (2,3).

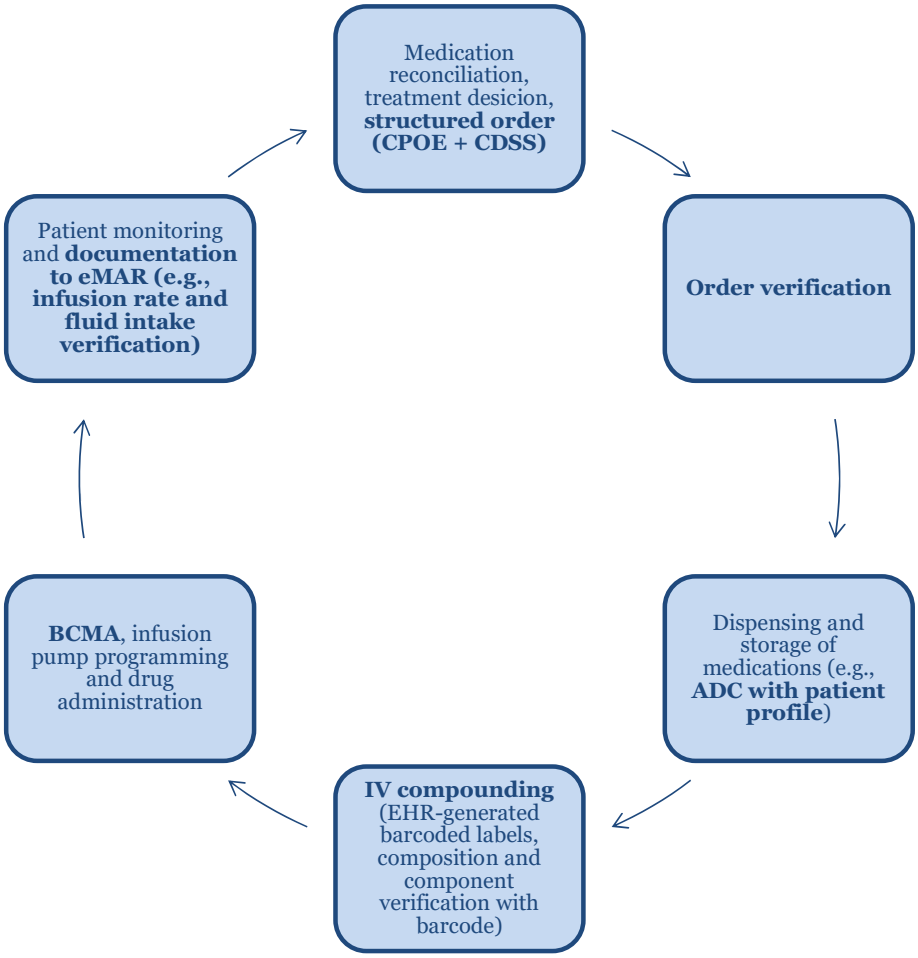

Figure 6. Intravenous (IV) medication use process in Helsinki University Hospital (HUS) (adapted from 2,3,35,75,83,88,103,118,119). ADC=automated dispensing cabinet, BCMA=barcode medication administration, CDSS=clinical decision support system, CPOE=computerized prescriber order entry, DERS=dose error reduction software, eMAR=electronic medication administration record.

A prescribing physician documents a structured order of IV medication, IV fluid, or parenteral nutrition to the EHR using standardized orders (Figure 6) (75). The use of verbal orders is restricted to resuscitation and emergencies. In some pilot wards, certain orders (e.g., high-alert drugs) are reviewed for appropriateness by a clinical pharmacist, a new way of working in Finnish hospitals (75,118). If an automated dispensing cabinet (ADC) is used in the unit, it is integrated into the EHR system and partially used in a profiled mode; thus, all drugs can still be removed using the override function (83).

In Finland, the availability of commercially manufactured, ready-to-use IV medications is limited, so most drugs are compounded in care units (Figure 6). The structured order determines the composition of each IV medication. EHR-generated labels include a patient and order-specific QR-code, and the components used in compounding are verified and documented to EHR using barcode technology (35). It is recommended to perform IV compounding in hospital pharmacies or biological safety cabinets located in the medication rooms in care units to ensure microbiological safety; thus, a lot of compounding is still carried out in patient care areas and medication room tables (51,53). Before administration, the right patient and the right drug are verified electronically by scanning a QR-code on the patient's wristband and the medication label (88,103,119). Drug administration is documented to the ERH at the patient's bedside. In the case of IV infusions, the possible pauses or changes in infusion rate are documented, and fluid intake from each IV infusion is carefully monitored and recorded during the treatment. The competence of registered nurses and ward pharmacists is ensured and documented by the employer before IV drugs can be compounded or administered independently (75,120). So far, there is no formal procedure to ensure the competence of doctors in Finland.

2.2.2 HIGH-ALERT MEDICATIONS

High-alert medications are drugs that bear a heightened risk of causing significant patient harm when they are used in error (9–11). Although mistakes may or may not be more common with these drugs, the consequences of an error are more devastating to patients. Identification and management of high-alert medications have been highlighted in WHO Global Patient Safety Challenge on medication safety and Joint Commission International (JCI) accreditation standards for hospitals (22,25,75). It is crucial to identify medication safety risks related to each drug and develop systemic defenses for error prevention (9–11,75,81,88,121).

ISMP has published lists of high-alert medications in different care settings, such as acute care (Table 8) (11). These lists are based on ME reports submitted to the ISMP National Medication Error Reporting Program (ISMP MERP), reports of harmful errors in the literature, studies identifying drugs most often involved in harmful errors, and input from practitioners and safety experts. Most ISMP high-alert medications in acute care settings are administered intravenously (Table 8).

Table 8. *Institute for Safe Medication Practices' (ISMP) list of high-alert medications for acute care settings with intravenous (IV) drugs bolded* (11). *IM=intramuscular.*

Classes/categories of medications
Adrenergic agonists, IV (e.g., EPINEPHrine, phenylephrine, norepinephrine)
Adrenergic antagonists, IV (e.g., propranolol, metoprolol, labetalol)
Anesthetic agents, general, inhaled, and **IV (e.g., propofol, ketamine)**
Antiarrhythmics, IV (e.g., lidocaine, amiodarone)
Antithrombotic agents, such as • **anticoagulants (e.g., unfractionated heparin**) • direct oral anticoagulants and factor Xa inhibitors (e.g., dabigatran) • **direct thrombin inhibitors (e.g., argatroban, bivalirudin**) • **glycoprotein IIb/IIIa inhibitors (e.g., eptifibatide)** • **thrombolytics (e.g., alteplase, reteplase, tenecteplase)**
Cardioplegic solutions
Chemotherapeutic agents, parenteral and oral
Dextrose, hypertonic, 20% or greater
Dialysis solutions, peritoneal and hemodialysis
Epidural and intrathecal medications
Inotropic medications, IV (e.g., digoxin, milrinone)
Insulin, subcutaneous, and **IV**
Liposomal forms of drugs and conventional counterparts (e.g., amphotericin B preparations)
Moderate sedation agents, IV (e.g., dexmedetomidine, midazolam, LORazepam)
Moderate and minimal sedation agents, oral, for children (e.g., chloral hydrate, midazolam, ketamine [using the parenteral form])
Opioids, including IV, the oral and transdermal route
Neuromuscular blocking agents (e.g., succinylcholine, rocuronium)
Parenteral nutrition preparations
Sodium chloride for injection, hypertonic, >0.9% concentration
Sterile water for injection, inhalation, and irrigation (excluding pour bottles) in containers of 100 mL or more
Sulfonylurea hypoglycemics, oral
Specific medications
EPINEPHrine, IM, subcutaneous
Epoprostenol (e.g., Flolan), IV
Insulin U-500 (Special emphasis even though all forms of insulin, SC and IV, are considered a class of high-alert medications.)
Magnesium sulfate injection
Methotrexate, oral, nononcologic use
Nitroprusside sodium for injection
Opium tincture
Oxytocin, IV
Potassium chloride for injection concentrate
Potassium phosphates injection
Promethazine injection
Vasopressin, IV, and intraosseous

There can be variations in the most important high-alert medications and medication safety risks associated with each drug between different specialties and care settings. For example, the most serious MEs in intensive care are associated with intravenously administered high-alert medications, such as catecholamines, insulin, electrolytes, opioids, and parenteral nutrition (Table 8) (32,33). Another example of a unique area is pediatric care settings, where high-alert medications have been investigated in a few studies and national guidelines (122–128). The minority is focused on neonates and NICU settings (128). It has been found that children are more likely to be exposed to high-alert drug-related prescribing errors than adults, with a child's weight not recorded or incorrectly recorded being the most common error (129).

In HUS, hospital-specific high-alert medications have been studied using the hospital's reports on MEs and ADRs compared with hospitals' drug consumption and the ISMP list of high-alert medications (39–41). After this step, an interprofessional expert group compiled an organizational list of high-alert medications for adult patients as part of the organizational patient safety strategy. High-alert medications at the entire hospital district level include antithrombotic agents, insulins, opioids, certain immunosuppressants, and oral anticancer drugs (39,40). Concentrated electrolytes were recently added to the list. In addition to these drugs, also other parenteral high-alert medications have been associated with a high risk for MEs (40,41). Some of them, such as radio contrast agents, cytotoxic drugs, propofol, and noradrenaline, are only used in selected units, which is why they do not appear on the general list.

Each specialty has been encouraged to supplement the general high-alert drugs with care area-specific medications. For example, high-alert drugs in all pediatric units also include parenteral nutrition, midazolam, and phosphenytoine (76). The pediatric list of high-alert medications was recently supplemented with IV sedatives administered to off-label routes (e.g., oral esketamine, intranasal dexmedetomidine, and intranasal fentanyl) and oral antihypertensive and cardiovascular drugs. Within pediatrics, the high-alert drug list is further supplemented by each specialty (e.g., neonatology, pediatric anesthesia, and intensive care) (130,131). In both adult and pediatric intensive care settings, area-specific high-alert medications include anesthetics and sedatives, cardiovascular drugs (IV), neuromuscular blocking agents (IV), and intrathecal or epidural drugs (131).

One important aspect of high-alert medications is look-alike sound-alike (LASA) drugs, which can get confused with each other in any step of the medication use process, exposing patients to wrong drug or wrong route errors (15,75,132,133). LASA names are medicine names that look or sound the same as other medicine names when written or spoken (75,133). Look-alike medicine packaging refers to medicine containers or primary packaging that looks like that of another medicine. LASA errors can lead to serious ADEs, especially when high alert medications are involved (9–11).

As an example, safe storage of LASA medications in ADCs has been investigated in HUS by observing the drug selection of one ADC machine located in an ICU (42). Approximately 70% of the drug selection was associated with a LASA risk with at least one other product, either by name or appearance of the drug package. Moreover, 20% of the LASA medicines identified were high-alert medications. High-risk situations arising from LASA naming, packaging, and labeling could be prevented by ensuring that LASA properties are checked thoroughly during prescribing, transcribing, procurement, storage, and dispensing (Figure 7) (15,75).

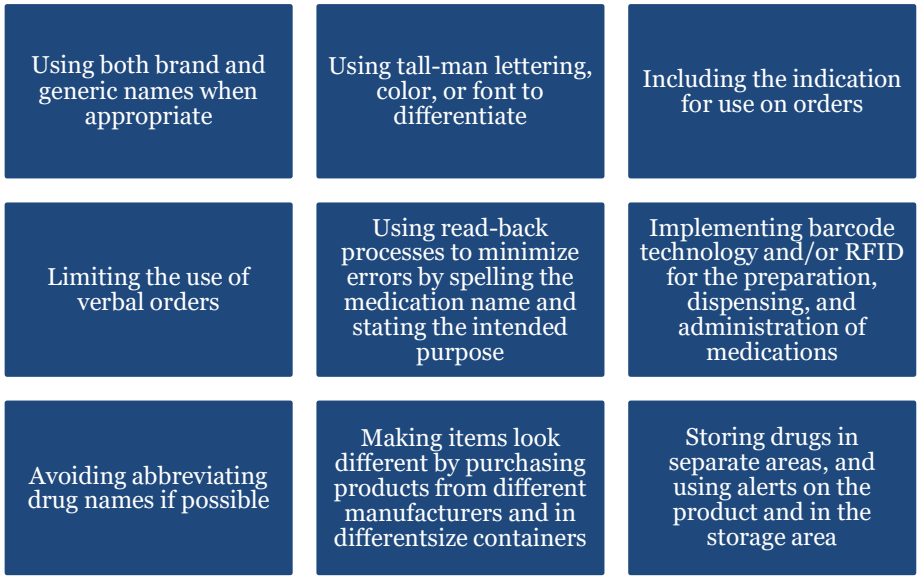

Figure 7. Strategies and recommendations for safe handling of look-alike, sound-alike (LASA) drugs in hospitals (15). RFID=radio frequency identification.

2.2.3 NEONATAL INTENSIVE CARE UNIT (NICU) AS A HIGH-RISK SETTING

2.2.3.1 Neonates as a high-risk patient group

Neonates are the group of children from birth up to and including the age of 27 days, including term and preterm neonates (Table 9) (17). The neonatal period is defined as a period from birth up to and including 27 days in term neonates, or from birth up to a post-menstrual age of 40 weeks and 27 days in preterm neonates. In Finland, 5.1% of children born in 2020 were born prematurely (<37 weeks) (134). Traditionally, premature babies weighing less than 2500 g have long been called preterm neonates. However, in the Finnish

Current care guideline of premature birth, preterm neonates are defined according to the weeks of pregnancy because of better clinical relevance (135). However, it might be appropriate to use different definitions or classifications depending on the context (e.g., weight-based classification is often used with drug dosing in neonates) (Table 9) (17). Within the preterm and neonatal ages, characterization of the weeks of gestation at the time of birth and after is relevant for understanding and applying phases of organ development (e.g., kidneys, liver) and determining drug doses (136).

Table 9. *The classification and definition of age in neonatal patients* (17,135). *Gestational age (GA) is defined as the time from the first day of the last normal menstrual period to the date of birth, expressed in completed weeks*$^{+\ days}$.

Definitions based on gestational age (GA)	
Term neonate	37^{+0} weeks of GA
Preterm neonate	< 37^{+0} weeks of GA
Extremely preterm neonate	< 28^{+0} weeks of GA
Very preterm neonate	28^{+0}–31^{+6} weeks of GA
Moderately preterm	32^{+0}–33^{+6} weeks of GA
Definitions based on birth weight	
Low birth weight (LBW)	Birth weight < 2500 g
Very low birth weight (VLBW)	Birth weight < 1500 g
Extremely low birth weight (ELBW)	Birth weight < 1000 g

The risk of potential ADEs resulting from MEs is significant in neonates, particularly in neonatal intensive care units (NICUs) (26,106,137). The NICU in HUS has 29 registered beds and round-the-clock preparedness to receive and treat premature and full-term neonates in need of intensive care (138). The most common causes for treatment are prematurity, respiratory difficulties, infections, complications in childbirth, malformations, neurological symptoms of the newborn, and problems of the newborn due to the mother's illness.

Several specific features expose neonatal patients to MEs and ADRs (Table 10) (17,25,26,136,139–144). Neonates are exposed to a higher risk of harm from MEs because of weight-based dosing, wide patient variability, rapidly changing body size and physical development, challenges to communicate with care providers, and more limited internal reserves to compensate for errors. As an example, the cardiovascular system of a premature baby may be unable to cope with even a small error in the dosage of an inotropic agent, and an accidental opioid overdose can lead to respiratory depression (106,128). During the neonatal period, there is physiological immaturity of organs, systems, and metabolic pathways that influence drugs' pharmacokinetics and

pharmacodynamics (142). Therefore, the medication dosage should be constantly amended, considering the progressive increase in weight and the maturation of the elimination pathways.

Table 10. *A synthesis of special features of the neonatal medication use process and examples of medication error (ME) risk factors identified in the literature* (17,25,26,136,139–144). *ADE=adverse drug event, ADR=adverse drug reaction.*

Special features	Examples of medication safety risks
Drug dosing based on weight (and/or gestational age)	• Erroneous, outdated, or unavailable weight and/or height. • Calculation errors and mix-ups in dosage units. • Errors in decimal points (e.g., 10-fold errors).
Wide patient variability	• Variation in patients' size (e.g., 10-fold variation in the neonatal intensive care unit, 500 g–10 kg). • Different needs of services (e.g., intensive care or monitoring in the ward).
Off label use of drugs	• The results of adult or pediatric clinical trials are not directly applicable to the neonatal population (e.g., dose recommendations, adverse effects, drug-drug interactions). • If scientific evidence is not available, information about drug use, efficacy and safety is based on clinical experience.
Lack of commercial drugs appropriate for neonatal patients	• Need for complex calculations, dilutions, and drug manipulation when medications formulated and packaged for adults or older children are used. • Harmful excipients (e.g., ethanol, propylene glycol, benzyl alcohol). • Extemporaneous preparations (e.g., oral suspensions, dose powders). • Using drugs without marketing authorization with special permission of the local authority.
Vulnerability to adverse effects	• Lower ability to physiologically tolerate a medication error due to the still-developing renal, immune system, and hepatic functions. • Rapidly changing body size and developmental systems.
Patients' limited capacity to communicate	• Neonates cannot communicate effectively to providers regarding responses to therapy, symptoms, ADRs, and possible ADEs. • Non-specific symptoms (e.g., variation in the intensity and pattern of crying) can be the only manifestations of some ADRs observed in neonates. • The clinical presentation of ADRs can be non-specific and be misinterpreted as the manifestation of a pre-existing condition. As such, these reactions will be less likely to be suspected and reported.

2.2.3.2 Medications used in neonatal intensive care settings

In NICU settings, it is often necessary to use medicines without a valid marketing authorization, indication, or commercial product for neonates (Table 10) (17,140,141,145–148). Off-label use indicates situations where a medicinal product is intentionally used for a medical purpose not following the terms and conditions of the marketing authorization (141). Relevant cases include the use of a drug indicated solely for adults or older children to treat neonates, possibly with a different dosage, different administration route, or a specific neonatal condition. Unlicensed medications are drugs lacking a market authorization in a specific country, such as imported drugs used in accordance with national regulations and extemporaneous medications prepared in a pharmacy (Table 10) (146,149).

A systematic review assessing the extent of the non-authorized use of drugs among hospitalized children found out that newborns received the highest percentage of off-label and unlicensed drugs, with a median use of 51% and 16% (148). Similar results were obtained in a Finnish University hospital in 2011, when the proportion of off-label prescriptions in newborns was found to be 51% and unlicensed medications 25% (145). However, in some sources the prevalence of off-label and unlicenced medication use in neonates has been estimated to be as high as 90% (17,147). Off-label use of medications in the pediatric population has been associated with a higher risk of adverse drug reactions (ADRs) than authorized use, with general anesthetics, patient's young age, and a high number of medications increasing the risk (150). However, the exceptional use of medicines in severely ill children is justified, especially when there is a long clinical experience or positive benefit-risk balance in high-level academic studies. In addition to active substances, some pharmaceutical excipients can be harmful to young children, especially neonates (Table) (151).

A recent systematic review exploring drug utilization patterns in NICU settings reported high and variable numbers of drugs used per patient (mean 4, ranging from 2 to 11), with several studies reporting use of more than 30 drugs in some infants (152). These findings are similar to a systematic review by Krzyzaniak et al. (2016) and a Finnish observational study by Lindell-Osuagwu et al. (2014) measuring the number of NICU patients' prescriptions in 2011. According to these two studies, premature infants were associated with more prescribed medicines per patient than term babies. The most common route of administration in NICUs is the IV route (47%–92% of products used), followed by the oral route (22%–23%). The drug utilization patterns are similar across most regions and nations (152). Antibiotics (e.g., gentamicin, ampicillin, vancomycin, amikacin, benzylpenicillin, cefotaxime) are the most widely used drugs in neonates, highlighting the importance of antimicrobial stewardship actions to prevent and control the spread of antibiotic resistance (75,152,153). Other frequently used medications include caffeine, multivitamins, furosemide, vitamin-K, surfactant, fentanyl, phenobarbital, theophylline, acetaminophen, iron, calcium, morphine,

aminophylline, sodium bicarbonate, dopamine, ranitidine, and heparin (152,153).

2.2.3.3 Medication use process in a neonatal intensive care unit (NICU)

The medication use process in NICU is particularly complex because of the use of high-risk administration routes, weight-based small dosages, multiple calculations and dilutions, common off-label use, and the use of unlicensed drugs (Figure 8; Table 10, p. 48) (26,128,145,154). As parenteral administration routes (e.g., IV) are widely used, the possible errors will often have a systemic effect (153). MEs resulting in 10-fold, 100-fold, and even 1000-fold overdoses have been reported in NICU settings. At the same time, such large deviations from the intended dose are less common in adult populations (see Figure 4, p. 28) (69,155–158). These errors can potentially cause long-term injury, such as developmental problems, toxic effects requiring active intervention, as well as even death (157). Moreover, many high-alert medications (e.g., opioids, insulin, vasoactive drugs, and parenteral nutrition), as well as drugs with narrow therapeutic index (e.g., vancomycin, gentamicin), are used in NICU settings (11,26,128,137). Factors that are more likely to result in harmful MEs include the use of high-alert medications, errors occurring in the prescribing phase, and equipment or drug delivery device failures (128). Proactive risk management strategies should be used to optimize these medication use processes of neonatal patients (Figure 8) (7,15,18).

MEs have been identified as a common problem in NICUs (ranging from 4 to 35 per 1000 patient-days, and from 6 to 78 per 100 medication orders) (137). Although the majority of reported MEs do not result in harm to the patient, MEs are common and often preventable (128,154). The medication use process phases most prone to errors are prescribing, administration, and drug preparation (26,137,154). Dosing errors are a prevalent error subtype in prescribing, transcribing, and administration, often occurring because of miscalculation of doses and incorrect placement of decimal points or units of measurement (Table 10, p. 48).

Lack of neonate-specific organizational drug protocols or policies has been identified as an important issue contributing to MEs, as off-label and unlicensed medicines are prevalent in NICU settings (Figure 8, Table 10) (26). Very small doses (e.g., many IV doses are less than one-tenth of a vial) complicate the drug preparation phase and increase the risk for large error magnitude, such as 10-fold errors. At administration, a NICU-specific ME type is patient misidentification because of similar-sounding or identical names and last names, difficulties in distinguishing multiple-birth babies (e.g., twins and triplets), and inability to communicate with patients. In a systematic review exploring interventions to reduce MEs in neonatal care, the greatest median reduction (73%) in overall MEs was seen with the use of technology-based interventions (e.g., CPOE and CDSS, IV administration technology, BCMA) (159).

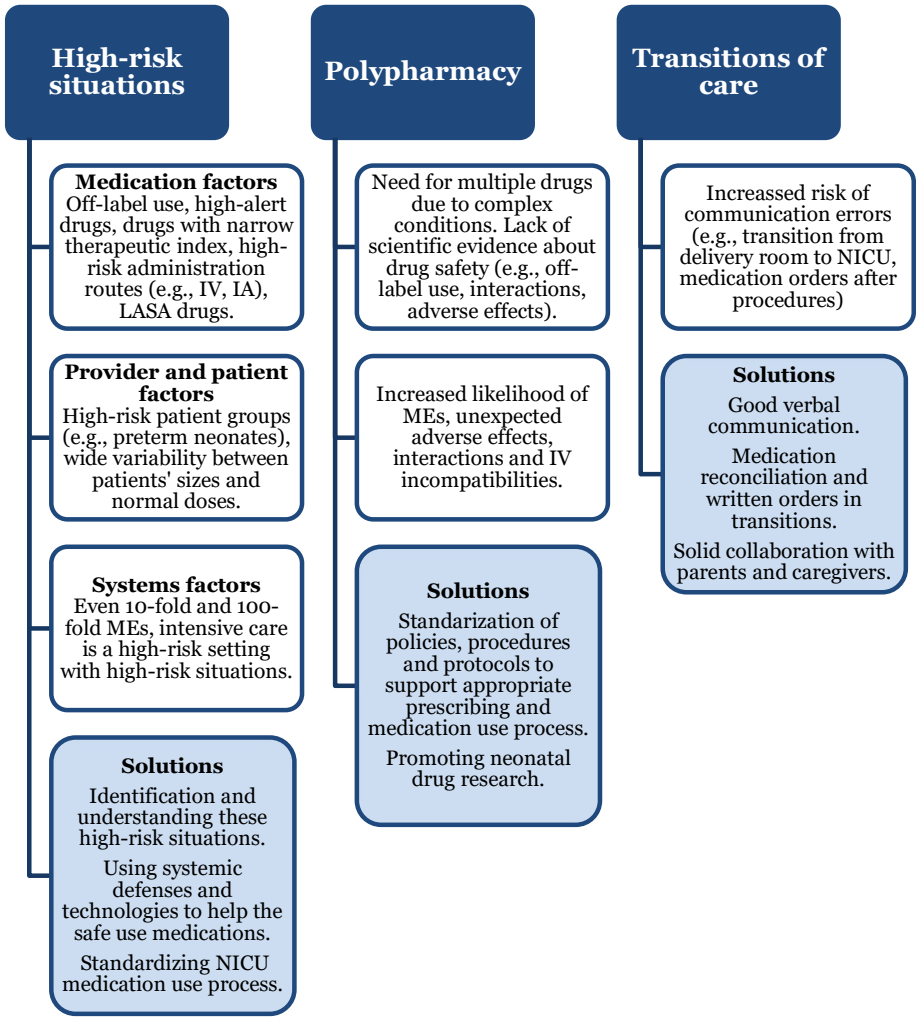

Figure 8. Special features of medication use process, medication safety risks and solutions in neonatal intensive care units (adapted from 17,22,25,26,39,128,153,154,160). IA=intra-arterial; IV=intravenous; LASA=look-alike, sound-alike; ME=medication error; NICU=neonatal intensive care unit.

2.3 SMART INFUSION PUMPS

Smart pumps are infusion devices with a decision support system, a dose error reduction software (DERS) (Table 11) (8). Key components of DERS are a drug library of standard medication concentrations, which alerts the user in case of significant errors (e.g., over- or under-delivery of medication or fluid), and capturing administrative infusion data in a systematic, objective manner to support system improvement. Smart pumps allow a greater level of control, accuracy, and precision in IV infusion delivery. The main differences between

programming a smart pump and a traditional infusion pump include selecting the drug and concentration to be administered from a drug library for the specific clinical area and responding to pump alerts (Table 11) (161).

Table 11. *Evolution and level of the implementation of smart infusion pumps* (adapted from 8,161,167). *BCMA=barcode medication administration, DERS=dose error reduction software, CPOE=computerized prescriber order entry, EHR=electronic health record, IV=intravenous.*

Level of smart pump implementation	Power
Smart pump interoperability with EHR • bidirectional integration with CPOE-system (e.g., auto-programming the pump according to physician's order, auto-documentation of the IV therapy to EHR) • integration with BCMA-system (e.g., assigning a pump to a specific patient)	
Drug library with DERS = smart infusion pump • specific drug library subsets (clinical area, patient groups) • standard infusion concentrations • patient group and care area-specific hard and soft dosing limits alerting in case of significant errors (e.g., in ordering, calculations, and pump programming) • continuous system improvement by utilizing infusion data	
Drug library without DERS • e.g., a list of IV infusion drugs, no system usage monitoring • no standardized infusions (e.g., care area and patient group-specific standard concentrations) • no dosing limits to catch pump programming errors	
No drug library • programming only the infusion rate and possible volume limitations to the pump • pump only alerting problems related to basic functions (e.g., empty syringe, infusion time ending, air or pressure in the IV-line, low battery)	

Although smart pumps are used in over 80% of the hospitals in the United States, they are not as widely used in Europe (8,162,163). However, the use of smart pumps can be expected to become more common, as they have been found to prevent serious MEs, such as even 29-fold drug doses in the NICU environment (164). In Finland, only a few drug libraries exist with configurations, not including all features stated in the ISMP's definition of smart infusion pumps and DERS (Table 11) (8). The highest level of systemic defense is reached when smart pumps are integrated into EHR (Table 11) (3,4,8,165). This feature is still rarely used in Europe, and a bidirectional

integration between smart pumps and EHR is not yet used in Finnish hospitals (166).

Successful implementation and maintenance of smart infusion pumps require continuous management, development, and monitoring of system performance, as well as user compliance (Figure 9) (8,161,167,168). ISMP has recently widened the recommendation to administer infusions via a programmable smart pump utilizing DERS from high-alert medications to all drug infusions (8,88,169,170). This approach emphasized the importance of ensuring the use of the DERS and planning for interoperability between an organization's infusion pumps and EHR. It applies to both inpatient and outpatient hospital settings. (E.g., magnetic resonance imaging [MRI] departments, emergency departments, outpatient infusion clinics), and to all situations in which medications are infused by the IV or epidural route, including anesthesia use and patient-controlled analgesia (PCA). The only exception is small volume vesicant infusions (i.e., chemotherapy). It should only be infused by gravity and not by a programmable infusion- or syringe-pump when administered via the peripheral route.

1. Leadership assigns responsibility by identifying a multidisciplinary project team or department (e.g., the pharmacy and therapeutic committee) responsible for smart infusion pump interoperability, including DERS, the oversight of drug library revisions or additions, infusion protocols, smart infusion pump maintenance, and related issues.
2. Define a process to create, test, regularly engage with and maintain a drug library.
3. Train and assess the competency of all clinical staff, including nurses and other clinicians who travel to various care settings.
4. Make the optimal use of DERS expected practice.
5. Monitor alerts, overrides, equipment or software recalls, adverse events, and close call reports.
6. If your organization has the capability, connect your smart infusion pump fleet with your EHR system.
7. Identify and address human and environmental factors — such as understaffing, variation in pumps that can create confusion in controls, workflow distractions, and low lighting or glare — that contribute to smart infusion pump programming errors in your hospital.
8. Keep the smart pump fleet safe from security threats and during downtime.

Figure 9. The Joint Commission recommends general actions that use a systems approach to help overcome barriers and optimize the safe use of smart infusion pumps with dose error reduction software (DERS) (167). EHR=electronic health record.

Smart infusion pump compliance rates should be monitored regularly. It is recommended to establish organizational expectations for using DERS to 95% or greater for the administration of medication infusions (including IV, epidural, and nerve block infusions) and IV fluid infusions (8,88). Many barriers to optimizing the use of smart pumps have been identified. These barriers include limitations in pump capabilities, alarm fatigue, availability of pumps, programming workflow, associated risks with secondary infusions, pump data analysis and persistent deficiencies related to library use and updates (e.g., omitting certain drugs and IV fluids and failing to engage the library for available drugs and IV fluids) (88,167,171). Additionally, barriers related to the usability of smart infusion pumps include confusing programming navigation, the need to toggle between multiple screens, unintuitive selection keys and menus, and poor ergonomics not supporting human factors and the end-user (172).

2.3.1 CONFIGURATION OF A DRUG LIBRARY

A comprehensive, well-functioning, and systematically maintained drug library is necessary to reach the benefits of smart pumps (Figure 10) (8,161,167). At the same time, the drug library should be uniform and still consider the different specialties and patient groups throughout the hospital. Building a drug library is a team approach and should include key stakeholders from at least the hospital pharmacy, nursing, prescribing, information technology resources, and EHR system (161,168). The leader for the drug library build is recommended to be a pharmacist with in-depth knowledge of the organization's drug formulary and IV infusion policies and procedures (168). Key components of the drug library are described in Figure 10.

Standardized policies for each drug infusion • standard concentrations and admixture preparation • standard dosing units and orders • alignment between EHR and drug library	**Creation of clinical care area-specific drug library subsets** • separate drug libraries for populations requiring similar medication concentrations • weight-based grouping of neonatal and pediatric patients
Dosing limits for different types of infusions • bolus/loading dose vs. continuous or maintenance infusion • use soft and hard dosing limits • establish dosing limits in drug policies and protocols	**Continuous drug library monitoring and evaluation** • use clinical advisories to discuss important issues and synthesize information • drug library development to reduce alert fatigue

Figure 10. Key components of a smart pump drug library (8,161,168).

The building of the drug library is started by identifying all medications that will be delivered using the infusion pump (168,173). The goal should be that all medication and fluid infusions are administered via a programmable infusion pump utilizing DERS (8,88). Thus, if smart pumps are not in use, it is essential to include IV high-alert medications into the drug library and DERS, as ISMP has recommended before (169,174). After creating a hospital master drug list, the clinical care area profiles can be used to customize standard concentrations, dosing limits, and other pump settings to specific clinical areas (e.g., NICU) (168,173). The drug information and nomenclature (e.g., drug name, dosing units, dosing rate) should be uniform throughout the drug library and the EHR systems to minimize confusion (8,88). It is recommended to use generic names to avoid the unnecessary need for drug library updates in case of changes in the hospital drug formulary. Tall-man letters can be used to prevent mix-ups between LASA-drugs (8,132,133,168).

The hospital should define a process to create, test, regularly engage with, and maintain a drug library (167). An interdisciplinary team approach is recommended to create, test, and maintain a drug library and update it periodically at a frequency to be determined by the organization (e.g., quarterly) (8,167). During the building and prior to implementation, independent double checks should be performed for every drug entry in the library, including drug name, dosing units, concentration, dose limits, and associated clinical alerts. A rapid approval process is recommended for new formulary additions, with appropriate checks and balances to ensure all safety considerations.

2.3.2 KEY COMPONENTS OF A DOSE ERROR REDUCTION SOFTWARE (DERS)

Standard concentrations are drug-specific standardized infusion concentrations used by the organization, which work as a base of drug library and DERS (Figure 10) (8,15,161,175,176). It is recommended to use commercial infusions whenever possible, as compounded IV medications are associated with a high risk for error due to added complexity and multiple steps required for determining the dosing when ordering, concentrations for preparation, and infusion rates for administering (8,89,91,175,176). The number of standard concentrations should be limited to one, no more than two for each drug included in the library for a specific patient care area or patient group (174–176). Using standardization as a quality improvement tool decreases variation, improves safety, and is the foundation for using clinical pathways and evidence-based guidelines. Standardization allows providers to manage excessive and unintended variations to customize patient care (175–177). At the organizational level, it is important to establish enough optional standard concentrations for different age groups (e.g., neonates, pediatric patients, adults) and care specialties (e.g., ICU, wards).

A drug library must include care area-specific dosing limits to catch critical pump programming errors (Figure 10) (8,161,162,168). Drug- or fluid-specific dosing limits can be placed to prevent both overdosing (upper limits) and underdosing (lower limits). While soft limits are intended to advise the user of potential errors and can be overridden, hard limits force functions to ensure that the facility-established medication-specific parameters are not exceeded. (E.g., the dose rate of continuous infusions, the dose of intermittent infusions, duration of intermittent infusions). Individual dosing limits should be defined for specific patient groups (e.g., neonates, pediatric patients, adults), clinical care areas (e.g., ICU, wards), and different types of infusions (e.g., loading dose, continuous infusions) (Figure 10).

2.3.3 SPECIAL FEATURES OF PEDIATRIC DRUG LIBRARIES

In pediatric care settings, medications are often dosed based on the patient's weight, and the size of patients can vary between a 500g neonate and a 100kg adolescent. Pediatric services encompass many types of patient care areas, such as NICU, pediatric intensive care unit (PICU), hematology and oncology, general medicine and surgery, bone marrow and organ transplants, newborn nursery, sedation, and emergency services. Commonly, IV infusion practices vary between pediatric patient populations and patient care areas, even within the same hospital or care system (173,175). Often, misperceptions exist that a specific area is unique and will not be able to standardize practice in such a way to enable the implementation of all safety-enhancing features of smart infusion pumps. Special features related to the building of pediatric drug libraries are presented in Table 12. Studies exploring smart pumps in NICU (164) or wider hospital settings treating neonates (178–182) have focused on describing the building of drug libraries at a general level and retrospectively evaluating drug library compliance or triggered alerts (Appendix 1).

The challenges related to pediatric standard concentrations include different needs than adult care areas, the lack of commercially available standardized products, wide weight and age ranges requiring more than one standard concentration, the need for the capability to administer small doses (e.g., syringe pumps), and the high prevalence of fluid restrictions (173,175,178,180,181). Standard concentrations administered via smart pumps eliminate the need for individualized dosage and rate calculations, simplify the IV infusion compounding process and simplify IV infusion ordering by the prescriber (173). According to a survey study, 40% of pediatric and neonatal units in the United Kingdom had established standard concentrations, with the use being more common in units caring for neonatal patients (61%) than those who are treating mainly pediatric patients (32%) (183). In the United States, there are national recommendations considering continuous infusion standard concentrations for neonates (184), children less than 50 kg (175), and adults and pediatric patients over 50 kg (176).

The dosing limits applied in pediatric drug libraries should be based on usual and maximum doses published in pediatric references and the primary literature (173,180). The need for each dosing limit type (lower hard, lower soft, upper hard, and upper soft) should be considered on a drug-by-drug and subset-by-subset basis. For instance, if a lower hard limit is not set for a particular drug by default, the lowest dose that can be delivered will be based on the lowest infusion rate the pump can deliver, which is dependent on the infusion device capabilities and institutional settings. Another important point of view is that the dosing limits are set in weight-based dosage units (e.g., mg/kg/h, microg/kg/min). For example, Carlson and Skoglund (2017) have used calculation formulas to define appropriate dosing limits in the pediatric drug library (Table 12) (173). Table 12 also summarizes examples of possible options regarding the decision about how to break down pediatric drug library subsets.

Table 12. *Special features related to the development of pediatric drug libraries* (173,175,180).

Area	Feature principles
Correct amount and distribution of drug library subsets	The options to break down drug library subsets include: • Age: neonates, pediatric patients (<45 kg), adults • Weight: e.g., Peds 0–5 kg, Peds 6–10 kg, Peds 11–20 kg, Peds 21–30 kg, Peds 31–40 kg, and Peds 41–50 kg • Pump type: syringe pumps, large volume pumps • Care areas: NICU, PICU, etc.
Definition of standard concentrations	• Whenever possible, one standard infusion concentration is the recommendation. • More than one standard concentration is recommended when it is necessary to accommodate patient care needs for extremely small neonates, fluid restrictions, differences required for peripheral versus central lines, to simplify calculations and accommodate limitations of pump infusion rates.
Appropriate dosing limits	• Based on usual and maximum doses published in pediatric references, dosing limits should be set in weight-based dosing units. • The soft limits can be determined by multiplying the low and high usual doses by 0.9 (lower) and 1.1 (upper). This method should allow for the prescriber rounding of doses. • The hard limits can be determined by multiplying the low and high usual doses by 0.1 (lower) and 1.2 (upper). Hopefully, these limits will prevent decimal errors in calculations or pump programming and other types of catastrophic under or overdosing.

2.3.4 INTEGRATING SMART INFUSION PUMPS TO CLOSED-LOOP MEDICATION MANAGEMENT SYSTEMS

A closed-loop medication management system is a process that ensures correct and adequate recording and transfer of information on the patient's medication by minimizing the risks associated with manual operations and information transfer (2). In the case of IV infusions, a closed-loop medication management system integrates CPOE, ADCs, BCMA, and smart infusion pumps together (Figure 11) (2–4,8,161). While the administration is one of the most error-prone steps of the IV medication use process (28,31–33,91), smart infusion pumps and a bi-directional smart infusion pump interoperability with the EHR are an essential part of IV closed-loop medication management systems (Figure 11) (3,4,8,161).

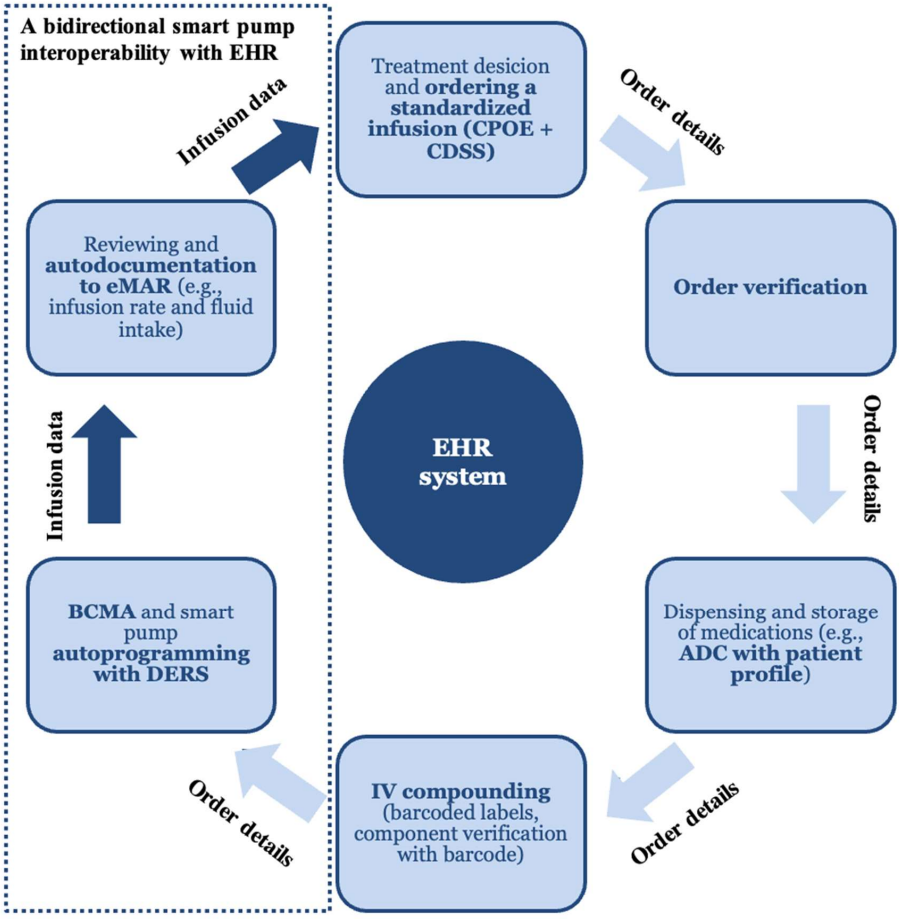

Figure 11. A closed-loop intravenous (IV) medication management system integrating computerized prescriber order entry (CPOE), automated dispensing cabinets (ADCs), barcode medication administration (BCMA), and smart infusion pumps (adapted from 2–4,8,161). CDSS=clinical decision support system, DERS=dose error reduction software, EHR=electronic health record, eMAR=electronic medication administration record.

The bidirectional interoperability between smart infusion pumps and the EHR system enables the transfer of order details to the infusion pump (e.g., drug, concentration, infusion rate), which the user must confirm prior to starting the infusion (Figure 11) (8,161). Likewise, the infusion data (e.g., rate changes, pauses, patient's fluid intake) returns from the smart pump to the EHR. Auto-documentation is an advantage, especially with critically ill patients on multiple IV infusions and pumps, as documenting their multiple infusions requires a considerable amount of time, is often delayed, and may introduce critical errors (4). Successful implementation can effectively reduce various ME types resulting from manual pump programming that still can occur with smart pumps (e.g., wrong concentration, infusion rate, drug, and patient weight) and reduce manual data entry steps (8). However, other types of systemic defenses are still needed to ensure IV medication safety. (E.g., oral syringes and epidural administration sets that do not fit to IV lines to prevent inadvertent IV administration of oral solutions and epidural medications) (34,108). As with smart infusion pumps alone, the introduction of interoperability with EHR has been associated with challenges, such as inadequate and outdated drug libraries, pump or medications not mapped with the EHR system, and inconsistency in dosing units between the drug library, EHR, and usual pump-programming practices (166).

2.3.5 DRUG LIBRARY IN HELSINKI UNIVERSITY HOSPITAL

The development of the first drug library maintained by HUS Pharmacy, the hospital pharmacy in HUS, started in 2018. At that time, drug libraries were still rarely used and undeveloped in Finland. Hospital pharmacists had limited theoretical expertise in the IV medication use process, smart infusion pumps, and drug libraries (185). The building of the drug library was initiated in the New Children's Hospital, which treats all pediatric diseases requiring specialist medical care in the Helsinki metropolitan area. In addition, the treatment of many demanding pediatric illnesses (e.g., cardiac surgery, organ transplantation, and severe cases of cancer) has been concentrated there.

The B. Braun Space system (Perfusor® Space syringe pumps and Infusomat® Space pumps) was used in all pediatric units, with a total amount of over 800 infusion devices. An interprofessional project team was established to set up the infrastructure for the building and implementation of the drug library (Figure 12). The neonatal intensive care unit (NICU) Saari located at Women's Hospital was chosen as a pilot unit due to the limited range of IV infusions used and the high utilization rate of standard concentrations. HUS Pharmacy was responsible for leading the building of the drug library. At the same time, HUS information technology experts, nursing experts, and pump vendors worked with the technical infrastructure (e.g., introducing new software to build and upload drug libraries to pumps, management of infusion devices).

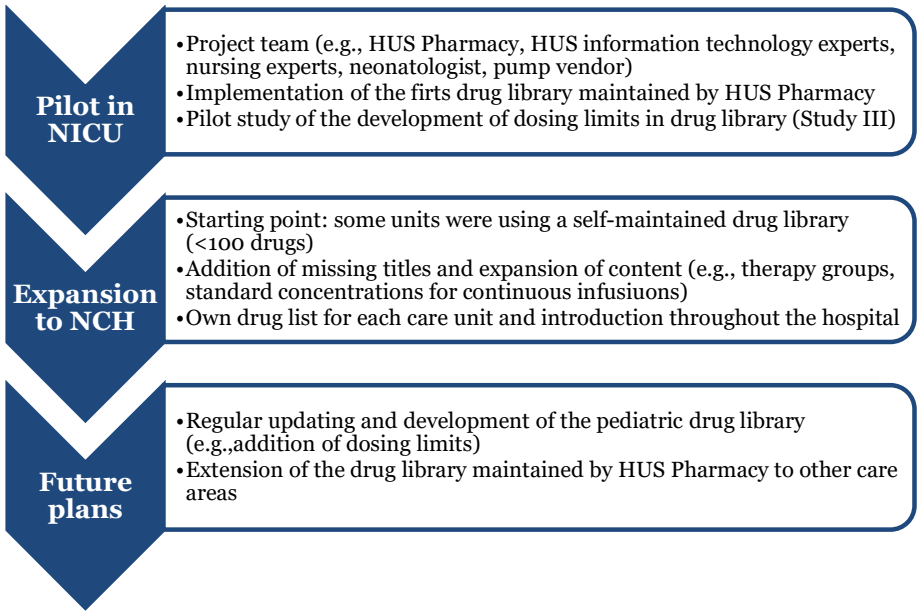

Figure 12. Development and implementation of a drug library maintained by HUS Pharmacy, the hospital pharmacy in Helsinki University Hospital (HUS). NICU=neonatal intensive care unit, NCH=New Children's Hospital.

Because of small drug dosages and infusion rates, Perfusor® Space (B. Braun Melsungen AG) syringe pumps are used to administer all IV infusions in HUS NICU. The first version of the NICU drug library, including therapy groups to help drug selection, generic names, and standard concentrations, was customized with B. Braun Space OnlineSuite software (AP 2.1.2) and implemented in November 2019 (Figure 12, Study III) (160). A pediatric clinic senior pharmacist performed the customization as a collaborative effort with a neonatologist, neonatal nurses, and medication safety officer. The implementation was evaluated based on user feedback and weekly follow-ups of drug library compliance.

Drug library compliance was measured with B. Braun DoseTrac® Infusion Management Software, which was at experimental use for almost half of the around 100 NICU infusion devices for nine weeks right after drug library implementation. The user feedback was positive, and drug library compliance was relatively high (mean compliance rate 81%); thus, lower than 95% recommended by the ISMP (8,88). To complement the first version, Study III was initiated to optimize the dosing limits for high-alert medications. Before Study III, without earlier experience of building a drug library, we found it hard to determine the proper range of dosing limits, because in the worst case, a poorly placed hard limit would prevent legitimate actions and, on the other hand, an unsuitable soft limit could cause useless alerts (Study II).

As a result of the positive experiences gained from the pilot, the wider implementation of the drug library was carried out in the New Children's Hospital (Figure 12) (186). A project pharmacist was allocated for a three-month project period in April 2021. The old drug library maintained by the units, New Children's Hospital's drug consumption report, IV infusion orders in EHR, and HUS pediatric medication guidelines were searched to identify all relevant IV infusions. The project pharmacist extracted IV medications, therapy groups, standard concentrations, and suggestions for the short names shown on the pump display to an Excel spreadsheet, which were double-checked with a clinic senior pharmacist (Table 13) (186). The drug library was built by transferring Excel information for Braun Online Suite software, and a care area specific drug list was formed for each care unit. Finally, the drug library was transferred to demo devices, and each drug was tested manually by the pharmacists. In addition, each care unit drug list was tested by the end-users. A medication safety newsletter describing the step-by-step use of an updated drug library was made to support the implementation. So far, the feedback from end-users has been mainly positive.

Table 13. *The drug library in New Children's hospital was first drafted into an Excel spreadsheet, after which the data was transferred to the pump vendor's building program (B. Braun Online Suite)* (186). *The first version of the drug library includes therapy groups, generic drug names, possible standard concentrations, and short names shown on the pump display.*

Therapy group	Medication	Standard concentration	Short name
Infections	Metronidazole	5 mg/ml	Metroni
Neurology	Methylprednisolone	no concentration	Mpredni
Antidotes	Methyltionine	no concentration	MetTio
Anesthesia	Midazolam	1 mg/ml	Midats1
		5 mg/ml	Midats5
Infections	Micafungin	no concentration	Mikafung
Heart and blood circulation	Milrinone	0,1 mg/ml	Milri0,1

At the time of writing this thesis, all pediatric units located at the New Children's Hospital had a uniform drug library updated to all infusion devices (Figures 12 and 13, Table 13) (186). The NICU located in Women's Hospital had its own infusion devices with a specific drug library (160). The next steps included drug library updates and dose error reduction software development, starting from high-alert medications (Figure 12) (160,186). We were also planning the extension of the drug library maintained by HUS Pharmacy to other care areas. Larger scale development aspects of smart infusion pumps

might include implementing a system enabling continuous drug library monitoring and evaluation, wireless infusion pump technology, and bidirectional smart pump interoperability with EHR (3,4,8,88,167).

Figure 13. An infusion pump in the New Children's hospital, when the uniform drug library maintained by HUS Pharmacy was used in 2021.

2.4 SUMMARY OF THE KEY FINDINGS OF THE LITERATURE REVIEW

- The hospital setting is considered as a HRO with culture of safety to learn from errors and implement systemic defenses for making the care safer. This has enabled a transition from retrospective error detection towards proactive risk management. In a just culture environment, safety is valued and continuously monitored. The accountability of errors is divided between the systems and the individuals. Powerful error-reduction strategies focus on changes to the system in which individuals operate instead of relying on human vigilance.

- Hospitals are regarded as high-risk settings in terms of associated risk for MEs during the care. High-risk situations arise from:
    - Medication-related factors, such as the use of high-alert medications,
    - provider and patient-related factors, such as MEs and high-risk patient groups (e.g., very young children), and
    - system-related factors, such as high-risk environments (e.g., NICU) and use of high-risk administration routes (e.g., IV route).

- IV drug administration is a multistep process posing safety risks if appropriate systemic defenses are not in place. MEs related to intravenously administered high-alert medications can lead to serious patient harm. For example, in HUS, some features of closed-loop medication management systems have been implemented to support IV medication safety.

- Neonates are exposed to a higher risk of harm from MEs because of their changing body size and physical development, challenges to communicate with care providers, and more limited internal reserves to compensate for MEs. Also, the medication use process in NICU is complex because of the wide use of IV administration routes, high-alert medications, weight-based small dosages, multiple calculations and dilutions, common off-label use, and the use of unlicensed drugs.

- Smart infusion pumps with DERS provide users with decision support to identify programming errors before starting the infusion. Successful implementation and maintenance of smart pumps require continuous management, system performance development and monitoring, user compliance. The building of drug library should be led by a pharmacist specialized in medication safety and IV drugs. The characteristics of each patient group (e.g., neonates) should be considered when building the drug library.

3 AIMS OF THE STUDY

The aim of this study was to support proactive medication risk management in hospital settings by focusing on improving safety of the intravenous (IV) medication use process. The study was divided in two phases. The first phase aimed to systematically summarize research evidence from the scientific literature on:

- systemic causes of IV medication errors (MEs) (Study I) and
- systemic defences, and their ability to prevent IV MEs to inform interprofessional medication safety activities (Study II).

The second phase focused on improving safety of IV medication in neonates as a high-risk patient group. The aim was to develop a method for defining and assessing optimal dosing limits in a NICU's smart infusion pump drug library by using simulation-type test cases that based on ME reports (Study III).

These objectives were derived and prioritized from the practical development needs of the Finnish healthcare system and hospital pharmacy practice as part of the care system. The aims are also in line with national and international initiatives to promote medication safety as part of patient safety (2,22,187–189).

4 MATERIALS AND METHODS

The empirical part of this dissertation consists of three original studies (Figure 14). Studies I and II were systematic reviews. The third study was a mixed-methods study utilizing ME reports as a starting point to develop simulation-type test cases to define dosing limits for selected IV high-alert medications included in the NICU drug library. The study applied a systems approach to medication risk management as a theoretical framework with the emphasis on just culture (7,15,19).

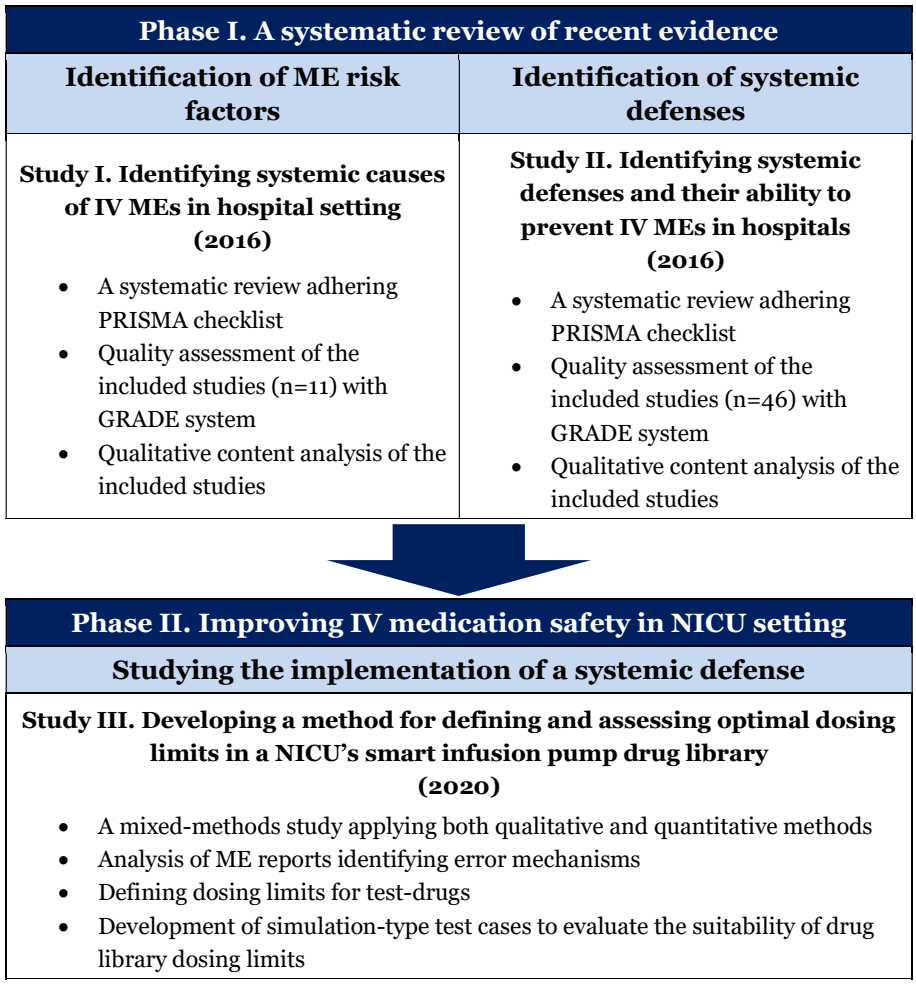

Figure 14. Outline of the study. GRADE= Grading of Recommendations, Assessment, Development, and Evaluations (191); IV=intravenous; ME=medication error; NICU=neonatal intensive care unit; PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses (190).

4.1 A SYSTEMATIC REVIEW OF INTRAVENOUS MEDICATION ERROR CAUSES (I) AND SYSTEMIC DEFENSES (II)

4.1.1 STUDY DESIGN

A systematic review of recent research evidence on systemic causes of IV MEs (I) and systemic defenses aiming to prevent these errors (II) in hospitals was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for undertaking and presenting systematic reviews (190). The quality of the included studies was assessed according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system (191). The included articles were analyzed using qualitative content analysis (192,193).

4.1.2 SEARCH STRATEGY

A systematic literature search was performed in June 2016 on MEDLINE (Ovid), Scopus, Cinahl, and Evidence-Based Medicine (EBM) Reviews covering the period from January 2005 to June 2016. This period was chosen to focus on the most recent research evidence published in peer-reviewed journals. An example of the search strategy is presented in Table 14.

The search terms were divided 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 the study objectives to explore preventable ADEs, which occur due to errors in the medication use process caused by omissions or commissions (14,31). The search strategy was completed with other terms similar to 'medication error' (Table 14), as inconsistency in terminology and definitions related to MEs is widely known (194). A combination of 'adverse drug event' and 'intravenous' was also considered. It was not included in the final search strategy because the combination resulted in a significantly large number of citations, emphasizing drug safety and adverse drug reactions without objectives relating to medication safety and the medication use process. We supplemented the search with a manual search of the reference lists of the included articles to identify all relevant publications.

Table 14. *Search strategy for the MEDLINE (Ovid) database (Studies I and II).*

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 years 2005-current

4.1.3 INCLUSION AND EXCLUSION CRITERIA

A predetermined PICO tool (participants, interventions, comparison, and outcomes) was applied to select studies for inclusion (190). A study was included if participants were hospitalized patients or the study utilized a patient scenario in a simulated hospital environment, and patients received IV medication. We decided to include simulation studies because clinical simulation enables the assessment of new systemic defenses in a safe and controlled environment without risk for patient harm (195). We excluded studies conducted in ambulatory settings, such as home infusion

chemotherapy, as we focused on in-hospital IV medication use processes. We also excluded studies focusing on multiple administration routes if the findings related to IV administration could not be reliably identified and extracted from the results. The comparison was not required, so we included studies utilizing both controlled and uncontrolled study designs. Studies applying measures associated with systemic causes of IV MEs (Study I) or assessing the systemic defenses intended to prevent these errors (Study II) were included. Studies exploring unpreventable ADEs or only incidence and types of MEs were excluded. Only English-language articles were included. Peer-reviewed journal articles utilizing all methods and study designs were included.

4.1.4 STUDY SELECTION

After removing duplicates, the search produced 1,417 potentially relevant publications (Figure 15). Two reviewers (SK, IN) independently selected studies based on the titles. In case of disagreement, the article was included in the next phase, in which the reviewers (SK, IN) independently selected studies based on the abstracts. Disagreements were resolved through discussion and consensus with a third reviewer (A-RH). The reviewers (SK, IN) independently selected studies based on the full texts of the remaining publications. The articles fulfilling the inclusion criteria of both reviewers were included (n=36). Disagreements were resolved through discussion and consensus with the third reviewer (A-RH), which led to the inclusion of nine more articles. A total of 45 publications met the inclusion criteria. Following this process, 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 IV MEs (Study I) and systemic defenses aiming to prevent IV MEs (Study II) (Figure 15).

4.1.5 DATA EXTRACTION AND ANALYSIS

Two of the authors (SK, IN) carried out data extraction and analysis, and the results were carefully reviewed by the other authors (A-RH, MA). In the study, I, study characteristics, country and setting, objectives, study design, materials and methods, key findings, and quality of evidence were extracted to a table (Study I: Supplementary File). In Study II, study characteristics, country, setting, study design, setting, evidence quality, systemic defense and comparison, number of patients (or other), primary measures, and key findings were extracted to a table (Study II: Supplementary file). We assessed the quality of the evidence using the GRADE system, which has four levels of evidence quality: very low, low, moderate, and high (191). Evidence from randomized controlled trials (RCT) and systematic reviews was graded as high quality, and observational data evidence was graded as low quality. For example, observational studies conducted in a simulated environment with a

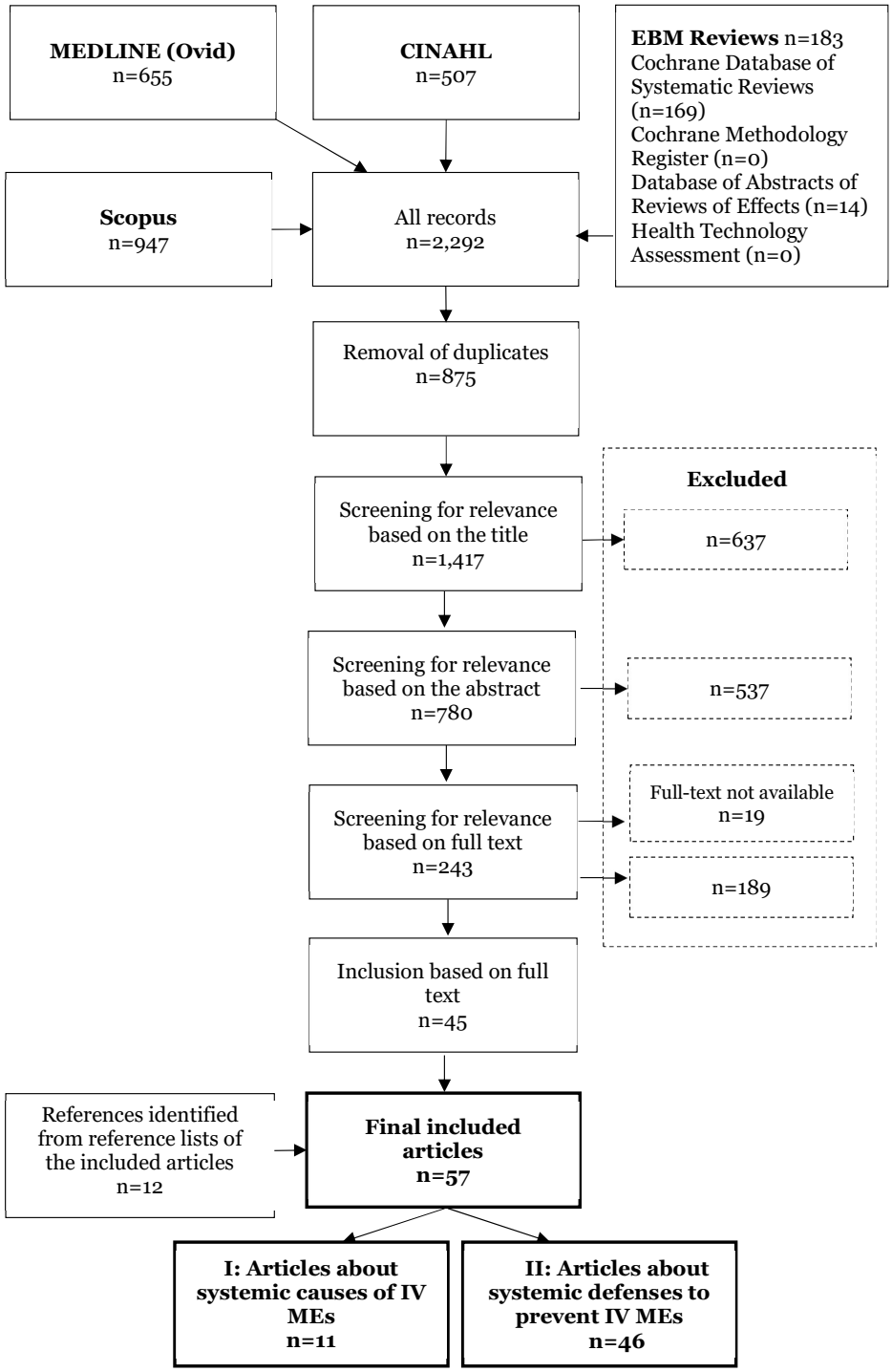

Figure 15. Flowchart of literature search for studies I and II.

small sample size was graded as low quality. Factors which 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 such as a large sample size, controlled study design, and multiple data collection methods and sources such as smart pump-produced log reports, chart reviews, staff reports, and incident reports) were also taken in account. Primary measures used in the articles were extracted to tables to demonstrate methodological variation between the included studies (Study I: Table 2; Study II: Table 2).

In Study I, we analyzed the contents of the included articles (n=11) using qualitative content analysis to identify systemic causes, examples of errors, and suggested systemic defenses for error prevention (Table 16, p. 73) (192,193,196). We used Leape's classic analysis of MEs as a foundation of our taxonomy (196). 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 modify the categorizations. Because we wanted to identify the most crucial systemic risk factors causing errors in the IV medication use 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. The systemic causes affecting more than one process stage were identified and presented in Table 15 (see p. 77).

In Study II, we analyzed the included articles (n=46) using qualitative content analysis to identify systemic defenses and their ability to prevent IV MEs (192,193). The findings were extracted and classified according to which medication process stage was most affected by the systemic defense mechanism (Study II: Table 3; Table 17, p. 84). The systemic defenses, evidence quality, and key findings are presented in Table 3 of the original Study II. We assessed the statistical significance of the key findings according to the possible statistical analysis presented in the articles, such as *P*-value ($P < .05$) and confidence interval (95% confidence interval excludes the null value). The authors' key conclusions and recommendations were extracted to Table 17 (p. 84).

4.1.6 UP-DATED LITERATURE SEARCH: THE MOST RECENT EVIDENCE (FROM 2016 TO OCTOBER 2021)

An additional up-date literature search on Medline (Ovid) database was performed in October 2021 using the same search strategy to review the most recent evidence (Table 14, p. 67). Studies published within the period from 2016 to October 2021 were included. One reviewer (SK) selected the studies based on titles, abstracts, and full texts (Figure 16). The search found 435

articles, of which 63 new articles were evaluated more closely. Studies I and II and the articles already included in them were excluded. The descriptions and main results of the included studies are presented in Appendixes 2 and 3.

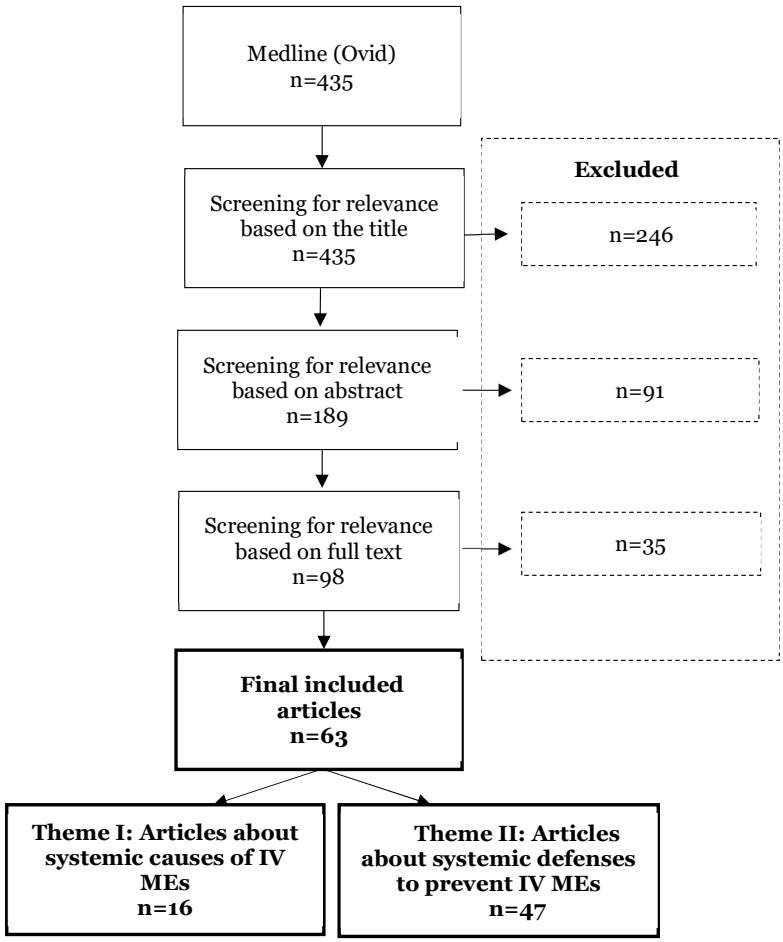

Figure 16. Flowchart of the additional literature search in October 2021 (Medline Ovid).

4.2 OPTIMISING THE DOSING LIMITS IN NEONATAL INTENSIVE CARE UNIT'S (NICU) INFUSION PUMP DRUG LIBRARY PRIOR TO IMPLEMENTATION (III)

4.2.1 STUDY DESIGN

This study was a mixed-methods investigation employing quantitative and qualitative research methods (197). The study was divided into three parts (Figure 17), starting with quantitative and qualitative analysis of register-

based NICU ME reports related to wrong infusion rate (Part 1) (7,192,193). In the second part, the results of the ME analysis were utilized to create simulation-type test cases with potential errors, and dosing limits were set to a test sample of selected IV high alert medications in the NICU drug library (Figure 17) (173,195). Finally, the test cases helped evaluate the appropriateness of the dosing limits quantitatively, including both right programming and potential errors. The study was based on the systems approach to risk management as a theoretical framework (7,19).

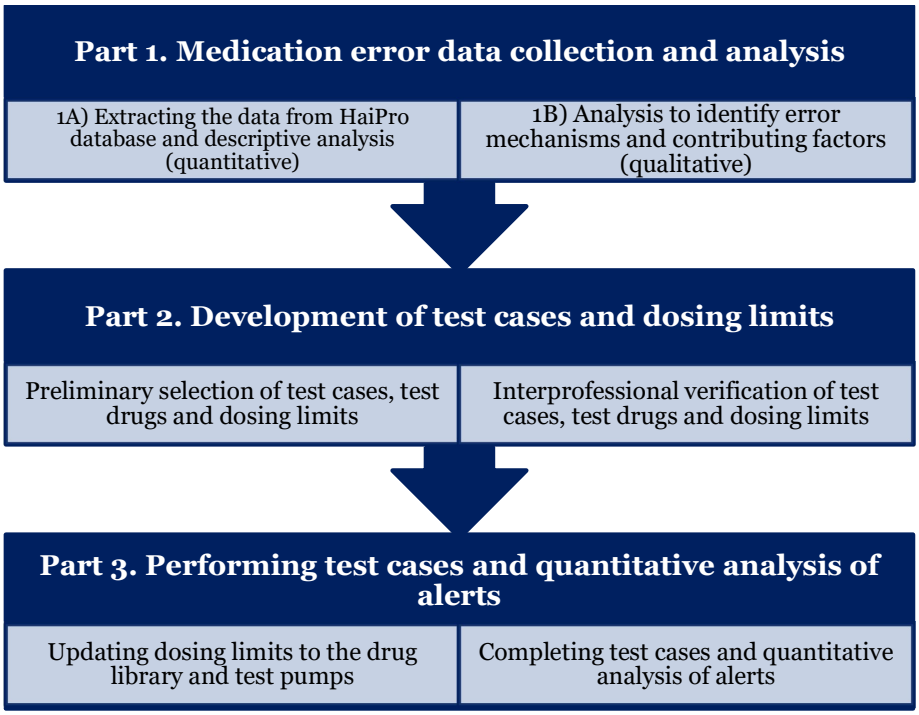

Figure 17. Flowchart of Study III.

4.2.2 STUDY SETTING

The study took place in the NICU in HUS, Finland, in 2020. The NICU has 29 registered beds and round-the-clock preparedness to receive and treat premature and full-term neonates in need of intensive care. Because most medications are used off-label, the approved use of every drug is described in the internal NICU medication guidelines. Perfusor® Space (B. Braun Melsungen AG) syringe infusion pumps are used to administer all IV infusions in the unit. Before this study, the first version of the NICU drug library, including therapy groups to help drug selection, generic names, and standard concentrations, was customized with B. Braun Space OnlineSuite software (AP 2.1.2) and implemented in November 2019 (see chapter 2.3.5, p. 59). The

customization was performed by a pediatric clinical pharmacist (SK) as a collaborative effort with a neonatologist, neonatal nurse practitioners, and a medication safety officer (CL-L, LS). This study was a part of the commissioning and programming of the drug library within the B—Braun Space system in the HUS NICU.

4.2.3 MEDICATION ERROR DATA COLLECTION AND ANALYSIS (PART 1)

In the first part of the study, the NICU ME reports related to wrong infusion rates were explored to identify possible mechanisms behind these errors (Figure 17) (7). The data were extracted from HaiPro, a voluntary and anonymous electronic reporting system for the patient- and medication-safety incidents largely used in Finland (43,44). It was introduced in HUS in 2007 and extended to all departments in 2011. All hospital staff members can submit the reports. The reports comprise both structured- and open-narrative information on errors, which responsible persons (usually a senior doctor and an assistant head nurse) trained for the task then coded in the units according to a certain structured classification system. MEs and near-misses reported in the NICU during 2018–2019 were extracted from the HaiPro database (LS). The reports related to wrong infusion rates were manually searched from the data by two researchers (KK, SK) independently. Only incidents identified by both researchers were included in the final research data. Disagreements on inclusion or exclusion of the error cases were resolved through discussion and consensus with a third researcher (A-RH).

The included ME reports were analyzed quantitatively and qualitatively (Figure 17, Part 1). Quantitative descriptive analyses reporting frequencies and percentages were performed to the structured data (Figure 17, Part 1A). The data comprised the medication involved in the error, event nature (e.g., ME or a near-miss), event type (e.g., prescribing error, administration error), the consequences to the patient, consequences to the unit, and the risk classification. In the HaiPro system, the risk classification of ME reports is determined on a scale of I to V (I=insignificant risk, II=low risk, III=moderate risk, IV=significant risk, and V=serious risk). The risk classification is based on the combination of 1) consequences of the injury to the patient (I=very minor, II=minor, III=moderate, IV=significant, V=severe) and 2) likelihood of error recurrence (I=rare, II=unlikely, III=possible, IV=probable, V=almost certain). Risk classification is used for identifying events posing a high risk to medication safety for further analysis in the healthcare organization using HaiPro. The researchers reviewed the original classification of the quantitative data (KK, SK) and corrected it, if necessary. In addition, the ISMP high-alert medications (11) involved in the ME reports were identified. The ISMP's acute care list was chosen because it is widely used internationally and applied in NICU settings (128).

The abductive qualitative content analysis was conducted to the open narrative data of ME reports to identify and categorize more specific error types, error mechanisms, and contributing factors (Figure 17, Part 1B; Appendix 4) (7,192,193,198). Two researchers (SK, KK) analyzed the narratives from the systems approach to gathering a more comprehensive understanding of the predefined issues (more specific error type, error mechanism, and contributing factors) associated with NICU MEs related to wrong infusion rates. These predefined issues were used as the main categories of data in the analysis. The findings were coded, and specific sub-categories were generated based on the data (Appendix 4). The size of the deviation from the intended dose was assessed when possible in the case of an overdose.

4.2.4 DEVELOPMENT OF TEST CASES AND DOSING LIMITS (PART 2)

In the second part of the study, test cases to optimize dosing limits were constructed by two researchers (KK, SK) based on the results of the ME analysis (Figure 17, Part 2). The identified ME mechanisms applicable to continuous infusions were utilized to develop test cases. The drugs selected for the cases in the analyzed ME reports were ISMP high alert drugs and were typically used in the NICU setting (11). In addition, these drugs have been identified as prone to pump-programming errors in other studies exploring smart infusion pumps in NICU and pediatric intensive care unit (PICU) settings (164,179,181). Preliminary upper soft limits for each test drug were defined by multiplying the highest usual doses by 1.1, as this coefficient allows the prescriber to round doses (173). Moreover, a 10% deviation of the reference dosage range has been identified as a dosing error threshold in PICU settings, as the evidence regarding NICUs remains limited (199).

In the HUS NICU, most continuous high-alert drug infusions are prescribed electronically in weight-based units (e.g., µg/kg/h), and the EHR calculates the infusion rate (mL/h) by utilizing the standard concentration (e.g., µg/mL) and patient's weight (kg). However, there may be a need to exceed the usual maximum dose in exceptional cases in intensive care. Therefore, only overridable soft limits were decided to be used in the study. According to previous studies in PICU settings where patients range from neonates to adolescents, it is particularly important to set weight-based dosing limits (180). The soft upper limits were placed in the drug library for each standard concentration in the same weight-based units as the drug is prescribed, and the patient's weight is entered into the pump before programming the infusion rate (mL/h). The identified error mechanisms, test cases, imaginary patients, drugs, and dosing limits were carefully reviewed and applied for the NICU's clinical practice by the research group, neonatologist, and neonatal nurse practitioners before proceeding to part 3 of the study.

4.2.5 PERFORMING TEST CASES AND QUANTITATIVE ANALYSIS OF ALERTS (PART 3)

In the last part of the study, the soft upper limits were loaded to the test pumps (Figure 17, Part 3). Two researchers (SK, KK) individually programmed the pumps simultaneously to verify flawless programming (one repetition/test case/researcher), first with the usual doses of the test drugs to ensure that there are no alerts without an error (Figure 18). After that, the pumps were programmed according to the error-containing test cases when alerts were desirable (one repetition/test case/researcher). Since the objective was to demonstrate whether there was an alert or not associated with each test case, there was not seen a need for a larger number of repetitions. The resulting alerts were documented and analyzed by descriptive statistics (frequencies, percentages) to determine the appropriateness of the soft upper limits.

Figure 18. In Study III, the test pumps were first programmed with the usual doses of the test drugs to ensure no alerts without an error. After that, the pumps were programmed according to the error-containing simulated test cases when alerts were desirable. An alert was displayed in the infusion pump screen when the soft upper limit was exceeded. The pump questioned too high an infusion rate, and the user needed to confirm whether to proceed or correct the misprogrammed infusion rate.

Study approval was obtained from the Helsinki University Hospital Joint Authority Administration. A separate ethics committee approval was not sought as the study did not contain any patient information or real patients.

5 RESULTS

5.1 SYSTEMIC CAUSES OF INTRAVENOUS MEDICATION ERRORS (I)

5.1.1 CHARACTERISTICS OF THE INCLUDED STUDIES

Study I was based on 11 peer-reviewed original articles (Study I: Supplementary File 1). The studies were conducted in the United Kingdom (n=4) (90,200–202), United States (n=3) (158,203,204), Spain (n=1) (205), France (n=1) (206), Republic of Korea (n=1) (207), and Canada (n=1) (208). All studies were carried out in a hospital setting. Three studies were conducted in NICUs (158,200,205) and three in adult oncology (202,206,208).

All the included studies applied an observational study design (Study I: Supplementary File 1). Four of the studies were retrospective analyses of ME reports (158,202–204), three were observational studies involving analyses of infusion concentrations (200,201,205), two were interview studies (90,207), one was a prospective analysis of medication orders (206), and one was a direct observation study (208). The three studies investigating infusion concentrations to detect preparation errors (200,201,205) used a controlled study design. More than one error detection method was used in two studies. One combined a video analysis of preparation technique and revision of preparation protocols with infusion concentrations analysis (205), and the other used interviews to complement direct observation (208). Six studies used self-reporting methods, such as voluntary ME reporting (158,202–204) and interviews (90,207). Study limitations were not reported, and their influence was not assessed in three studies (200,201,207). None of the included studies applied RCT design, so they were graded as low quality (191).

The measures used to identify causes of IV MEs in the studies varied, but some shared measures were identified (Study I: Table 2). Actual or potential causes of errors (n=7) and the principal defenses that had been breached by each incident (n=1) were used in studies focusing on a larger scale of MEs in multiple process stages. The concentration accuracy of prepared infusion solution (n=3) was used to identify preparation errors in studies comparing different ways of preparing IV medications to identify ME risk factors. Three studies also focused on contributing factors to MEs (90,158,204).

5.1.2 SYSTEMIC CAUSES OF MEDICATION ERRORS AND POTENTIAL SYSTEMIC DEFENSES FOR ERROR PREVENTION

The studies identified systemic causes of IV MEs related to prescribing (n=6 studies), preparation (n=6), administration (n=6), dispensing and storage (n=5), and treatment monitoring (n=2) (Tables 15 and 16). The process stage with the most ME causes identified was administration (90,158,202–

204,207). The manual adjustment of infusion rates for each patient is an especially high-risk task, leading to wrong dose errors (158,204,207). A pump programming error can occur as a consequence of confusion between hours and minutes (e.g., 20 min instead of 20 h), weight and volume (e.g., order 5 mg/10 min, programmed 5 mL/10 min), decimals (e.g., order 0.5 mL/h, programmed 5.0 mL/h), volume and time (e.g., 24 mL instead of 24 min), syringe sizes (e.g., 20 mL intended, 30 mL used and programmed), or two drugs' infusion rates (158,204). Some causes enabled MEs in more than one process stage (Tables 15 and 16). Insufficient actions to secure safe use of high-alert medications (90,202,207) and lack of knowledge of the drug (90,200,201,204,205,208) were identified as the two causes, which affected the most process stages, followed by calculation tasks (203–205), and confusion between LASA-drugs (90,203,204,206). The studies also pointed out that the absence of a systemic defense, or an existing defense breaking down, can enable errors (e.g., failures to review orders after prescribing or to double-check during the preparation and administration) (90,206,208).

Table 15. *The most crucial systemic causes resulting in intravenous medication errors in more than one medication use process stage (Study I). CPOE=computerized physician order entry, CDSS=clinical decision support system, LASA=look-alike sound-alike.*

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

In all the studies (n=11), potential defenses for IV ME prevention were suggested (Table 16). 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 MEs and improve error detection (90,158,200–202,204–208).

Table 16. *Systemic causes of intravenous (IV) medication errors (MEs) and potential systemic defenses (Study I). ADC=automated dispensing cabinet, CDSS=clinical decision support system, CPOE=computerized prescriber order entry, IT=intrathecal, LASA=look-alike sound-alike, PCA=patient-controlled analgesia.*

Error type	Systemic causes and examples of medication errors (MEs)	Potential systemic defense for error prevention
Prescribing (ordering, transcription, and order verification) (n=6 studies)		
Wrong drug	LASA drugs; communication errors: choosing a wrong drug (e.g., a sound-alike drug), confusion with drug name because of verbal prescription	Incorporating medical consultation and multidisciplinary reports to CPOE Standardized procedures for high-alert medications and emergencies
Wrong dose	CPOE and CDSS: 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) Communication errors: confusion with the dosage because of verbal order Calculation tasks: 10-fold errors, failure in dosage conversation	Pharmacist's analysis of orders and duplication of the previous order in CPOE Standardized procedures for high-alert medications and emergencies Increasing vigilance and adapting alarms to the needs of prescribers Using conversion charts to reduce the need for calculations Documented independent double-checks for calculations
Wrong route	CPOE and CDSS: the possibility to choose the wrong route (e.g., IT instead of IV)	Not reported
Extra dose	Lack of standardization; CPOE and CDSS: inaccurate date or treatment regimen	Standardization of schedules and utilization of CPOE
Wrong choice	Lack of knowledge of the drug: failure to adjust the dose to comorbidities (e.g., renal impairment, sleep apnea) or other drugs (e.g., opioid and multiple CNS drugs) Lack of patient data; high-alert drugs: PCA to patient unable to use it properly	Full training of practitioners before they participate in high-risk processes (e.g., prescribing PCA)
Multiple error types	CPOE and CDSS: failure in documentation (e.g., wrong patient or treatment setting; incomplete, illegible, contradictory, or duplicated orders, order forgotten or documented in the wrong place) Failure to double-check: overconfidence, casual attitudes, or deciding not to question prescriber (e.g., a respected physician, other people not available)	Pharmacist's analysis of orders within the CPOE system System simplification Equal responsibility and empowerment to challenge prescriber Education, training, and increased access to supportive resources
Dispensing and storage (n=5 studies)		
Wrong drug	LASA drugs; high-alert drugs: e.g., morphine and HYDROmorphone, sound-alike drugs during product shortage, misfills of ADCs (e.g., wrong concentration or wrong product in machine's pocket)	"Tall-man" lettering to help visually distinguish between similar packages ADC directly linked to pharmacy information systems Not overriding prompts from ADC without consulting a pharmacist

	High-alert drugs: too easy availability of high-alert medications (e.g., storing IT and IV drugs together, or undiluted electrolytes in wards and patient carts)	Independent double-checks of products by two individuals Separate storage of high-risk route drugs (e.g., IT doses in a locked fridge) Maintaining adequate product inventory for patient care Interprofessional resolving of differences between products and order
Preparation (n=6 studies)		
Wrong drug or diluent	Similar looking equipment: preparing multiple medications at the same time and storing them in close proximity (e.g., incorrect labeling) Lack of knowledge of the drug: incorrect type of diluent for reconstitution	Entering only one preparation to the biological safety cabinet at a time Pairing label and instructions with preparation supplies and the final product An independent double-check of diluent type during preparation
Wrong dose	Calculation tasks: no standard concentrations (e.g., other strength of replacement infusion, using standard volumes makes doses unique) Problems related to drug product: 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) Lack of knowledge of the drug: incorrect volume (e.g., wrong syringe size)	Documented independent double-checks of calculations Implementation of standard concentrations to eliminate calculation errors Using bulk solutions prepared aseptically in the pharmacy Using right-sized syringe in volume measurements Drug manufacturers' and syringe providers' compliance with current legislation An independent double-check of diluent volume during preparation
Wrong technique	Lack of knowledge of the drug: incorrect mixing or insufficient reconstitution time (e.g., overdose or too low dose because the drug was not uniformly distributed in the syringe or infusion bag)	Educational interventions about correct preparation technique Using electrolyte solutions prepared commercially or aseptically in pharmacy Vigorous mixing and using bags rather than syringes for electrolyte solutions
Multiple error types	Failure to double-check: 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	Equal responsibility and empowerment to challenge prescriber Education, training, and increased access to supportive resources
Administration (n=6 studies)		
Wrong drug	LASA drugs; similar-looking equipment: several injection lines on a single fluid hanger, confusion between LASA medications	Barcode medication administration systems Independent double-checks of products by two individuals
Wrong dose	Calculation tasks: 10-fold errors, confusion between weight and volume (e.g., 1 mg ordered, 10 mg/mL used, 1 mL given), products with different concentrations (e.g., pump not reprogrammed when starting replacement infusion) Problems related to drug product: too low dose because more than one ampoule is needed for one dose Infusion device problems: wrong infusion rate because of a pump programming	Smart-pumps including a drug library and safety-alerts Standardizing infusion pumps (e.g., pumps from a single manufacturer) Documented independent double-checks for right pump settings and validation of infusion rates at shift change Restricted amount of PCA drugs to avoid confusion on the PCA pump's screen Consult reference material for each drug during setup (e.g., dosing cards) Clear labeling (e.g., drug concentration prominent and clearly legible)

	error, wrong programming of other PCA pump variables (e.g., bolus dose, lockout interval) High alert drugs: patient's family member activating PCA (e.g., overdose risk)	Educating staff and family members about the proper use of the PCA pump
Wrong route	LASA drugs; 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) High alert drugs: inadequate separation of IT and IV drugs in time or location (e.g., same administration day, storing them together)	Awareness of the possibility of tubing misconnections, tracing the origin of tubing to insertion or connection to ascertain the proper location of each tube Documenting infusion pump tubing at shift change Separating IV and IT drugs in time, location, and appearance (e.g., IV vinca alkaloids prepared in mini-bags to avoid accidental IT administration)
Extra dose	CPOE and CDSS; communication errors: failure to record drug administration, unauthorized drug (e.g., wrong patient or unordered drug)	Not reported
Missed dose	Infusion device problems: tubing disconnected or never connected to the patient, pump not turned on, interrupted infusion not resumed CPOE and CDSS: orders for therapy overlooked	Documented verification of orders, validation of infusion device settings, and a trace of infusion pump tubing at shift
Equipment failure	Infusion device problems: insufficient pump settings (e.g., not allowing infusion < 1 mL/h), device shortage or malfunction Lack of knowledge of the drug: removing the light-resistant wrapping	Not reported
Multiple error types	Failure to double-check: distractions, poor instructions of which things should be checked, not checking thoroughly (e.g., a task carried out with a trusted colleague)	Education, training, and increased access to supportive resources
Treatment monitoring (n=2 studies)		
Inadequate monitoring	Lack of knowledge of the drug; high alert drugs: knowledge gaps (e.g., serious adverse effects, high-alert drugs), no support resources, or not using them	Education, training, and increased access to supportive resources Safety guidelines, evaluation, and education for high-alert medications

For a detailed presentation of references, please see the original Study I.

5.1.3 UP-DATED LITERATURE SEARCH: THE MOST RECENT EVIDENCE ON SYSTEMIC CAUSES OF INTRAVENOUS MEDICATION ERRORS

The additional up-date search on Medline (Ovid) database found 16 new articles describing systemic causes of IV MEs (Appendix 2). The studies were conducted in 6 countries, which included United States (n=6) (94,209–213), United Kingdom (n=5) (214–218), France (n=2) (219,220), Canada (n=1) (221), South Korea (n=1) (222), and Spain (n=1) (223). Most of the studies were conducted in hospital setting (n=7) (94,211–213,215,216,222), and some in pediatric hospital setting (n=3) (214,218,219), hospital pharmacy (n=2) (210,221), emergency department (n=1) (209), ICU and hematology sterile unit (n=1) (220), NICU (n=1) (223), and simulated pediatric medical facility (n=1) (217).

There was a lot of variation between the study designs and research methods. The methods used in more than one study were observational methods (n=7) (94,215–218,220,221) and retrospective analysis of ME reports (n=2) (213,214). Other methods included a systematic review (n=1) (211), analysis of IV compatibility data in literature (n=1) (223), failure mode and effects analysis (FMEA) (n=1) (210), inductive preliminary hazard analysis (n=1) (219), retrospective analysis of smart pump alert data (n=1) (212), retrospective analysis of medical records (n=1) (222), and structured chart and video review (n=1) (209).

Some themes related to systemic causes of IV MEs appeared in more than one study, and these included risks related IV preparation worklflow and technology (n=3) (210,218,221), smart infusion pumps (n=3) (94,211,212), IV compatibility (n=2) (220,223), and preparation and administration of IV push doses (n=2) (209,219). Other risk cathegories included errors throughout the IV medication use process (n=1) (213), IV fluid prescribing (n=1) (214), IV medication guidelines (n=1) (217), postoperative patient controlled analgecia (PCA) (n=1) (222), procedural and documentation deviations related to IV infusion administration (n=1) (216), and residual volume for different IV administration sets (n=1) (215).

5.2 SYSTEMIC DEFENSES TO PREVENT INTRAVENOUS MEDICATION ERRORS (II)

5.2.1 CHARACTERISTICS AND MAIN OUTCOMES OF THE INCLUDED STUDIES

The systematic review exploring systemic defenses to prevent IV MEs was based on 46 peer-reviewed original articles (Study II: Supplementary File 1). The studies were conducted in 11 countries, which included the United States

(n=22) (162,178,224–243), Canada (n=8) (244–251), Germany (n=4) (252–255), the United Kingdom (n=3) (256–258), New Zealand (n=2) (259,260), Spain (n=2) (181,261), Australia (n=1) (262), Brazil and the United States (n=1) (263), France (n=1) (264), Israel (n=1) (265), and Korea (n=1) (266). Altogether, 30 studies (65%) were carried out in North America. Most of the studies were conducted in a hospital setting (n=34) (178,181,224–226,228,230,232,234–239,242–248,252–255,257–265), and some in simulated hospital environments (n=11) (227,229,231,233,240,241,249–251,256,266). One study was a systematic review including studies conducted in a hospital setting and in a simulated hospital environment (162).

There was a lot of variations between the study designs and the evidence quality of the studies. Of the 46 included articles, 38 (83%) (178,224,225,227,229,231–242,244–253,255–262,264–266) involved a controlled study design. Only 2 studies (4%) were graded as high quality: of these 2, one applied an RCT design (259) and the other was a systematic review (162). Six studies (13%) (237,239,242,247,248,260) used a controlled observational study design with large magnitude of effect, which is why they were graded as moderate quality. Four of these were analyses of incident reports, ME reports, or ADE data (237,239,248,260) and 2 were observational reviews of patient records (242,247). The remaining 38 studies (83%) (178,181,224–236,238,240,241,243–246,249–258,261–266) applied an observational study design without large magnitude of effect, which is why they were graded as low quality. Controlled low-quality studies (n=31) applied variable designs: simulation studies (n=11) (227,229,231,233,240,241,249–251,256,266), observational reviews of drug charts, medication orders, or patient records (n=11) (224,225,232,234–236,244,246,252,253,258), studies combining multiple methods (n=4) (257,262,264,265), analyses of ME or ADE data (n=3) (178,238,245), and analyses of infusion concentrations (n=2) (255,261). Some low-quality studies (n=7) (181,226,228,230,243,254,263) used an uncontrolled study design. The study limitations were not reported, and their influence was not assessed in 5 studies (11%) (243,248,258,263,264).

The primary measures used in the included studies varied, but some shared measures were identified (Study II: Table 2). The measure most widely used to assess the effectiveness of a systemic defense was the incidence of MEs, which appeared in 25 studies (54%) (178,224,226,227,229,231–233,235,238,240,245–249,251,255,256,258–261,265,266). There were many variations among the ME detection methods used, making it difficult to compare results between the studies. Measures quite similar to MEs, such as ADEs and clinical incidents (n=5) (237,242,260,262,264), potentially prevented MEs (n=4) (181,228,243,254), and serious MEs (n=2) (233,239) were used in 11 studies (24%). Time to task completion appeared in 12 studies (224,227,229,231,233,240,241,256,264–266), and it was a commonly used measure especially in simulation studies.

5.2.2 SYSTEMIC DEFENSES AND THEIR ABILITY TO PREVENT INTRAVENOUS MEDICATION ERRORS

Systemic defenses, their ability to prevent IV MEs, and statistical significance of the key findings are presented in Table 3 of the original Study II. Key conclusions of the included studies and recommendations presented by the authors are presented in Table 17. Of the systemic defenses identified, most were related to administration (n=24 studies; 52%) (162,178,181,227–229,233,235,239,241,243,245,249–254,257,259,260,263,264,266), followed by prescribing (n=8; 18%) (224,232,236,242,246,247,258,265), preparation (n=6; 13%) (226,230,238,255,256,261), treatment monitoring (n=2; 4%) (225,234), and dispensing (n=1; 2%) (240). Five studies (11%) (231,237,244,248,262) focused on high-risk process standardization and involved implementation of systemic defenses related to multiple medication use process stages.

Systemic defenses, including features of closed-loop medication management systems, appeared in 61% of the studies (n=28; Figure 19) (162,178,181,225–228,231,232,234–241,243,245,250,254,255,257–260,264, 265), with smart pumps being the systemic defense most widely studied (n=11; 24%) (162,178,181,228,235,239,243,245,250,254,264). Besides preventing prescribing errors, CPOE and CDSS were found to contribute toward safe dispensing (240), administration (227,231,241), and treatment monitoring (225,231,234) by preventing MEs related to interpretation of orders, calculation tasks, and follow-up. In addition to systemic defenses related to closed-loop medication management systems, prefilled syringes (233,256) and color-coded systems (229,233,266) were found to reduce errors in high-risk environments and situations, such as operating rooms and resuscitation.

Although smart infusion pumps were the systemic defense most widely studied, their effectiveness in ME prevention remains unclear (Table 17; Study II: Table 3). The key component of the smart pump is a drug library containing predefined parameters for the drug type, strength, and dosing limits of specific drugs. Soft limits are alerts that clinicians can override, whereas hard limits cannot be overridden. Insufficient compliance in drug library use is problematic, as the systemic defense is not active if the drug library is bypassed (162,181,239,254). Another issue is the high override rate of soft limits, which, unlike hard limits, do not require changes to pump programming when the patient is at risk of getting a wrong dose (228,235,239,243,245,250,254,264). Opportunities for improvement include using hard limits and integrating smart pumps with other systemic defenses, such as barcode readers and CPOE real-time clinical data (e.g., glucose control and respiratory monitoring) (162,181,228,235,243,250,254).

Table 17. *Conclusions and recommendations presented by the included studies' authors (n=46) (Study II). CPOE=computerized physician order entry, CDSS=clinical decision support system, EPS=enhanced photoemission spectroscopy, IV=intravenous, ME=medication error, PCA=patient-controlled analgesia, SICU=surgical intensive care unit, SOP=standard operating procedure.*

Process stage	Key conclusions and recommendations
Prescribing (n=8 studies)	A standard order form increases order completeness and reduces prescribing errors and patient harm. Online calculators improve prescribing in complex dosing policies (e.g., obese and pediatric patients) and eliminate high-risk errors. A customized alert significantly decreases inappropriate prescribing, but providers may abandon an appropriate prescription in response to an alert. CPOE and CDSS generated resuscitation orders are legible, complete, automatically checked for accuracy, and completed in less time. When a pharmacist is present, patients are more likely to receive appropriate doses of antimicrobials more quickly. A multidisciplinary approach involving simple interventions resulted in improved physician prescribing behavior.
Dispensing (n=1 study)	CPOE orders saved pharmacists' time and improved the safety of processing continuous infusions, although not all errors were eliminated.
Preparation (n=6 studies)	Compounding workflow software systems (e.g., barcode scanning, gravimetric weighing of components, real-time images of process steps) improve detection of preparation errors. Centralized, automated preparation of standardized infusion solutions may effectively reduce clinically relevant deviations in concentration conformity of infusion solutions. Providing drug infusions in syringes pre-filled by pharmacists or pharmaceutical companies would reduce MEs and treatment delays. Calculation errors can disappear with good standardization protocols, but accuracy errors depend on good preparation techniques and environmental factors. A tabletop EPS device demonstrated sensitivity and specificity in validating the identity and concentrations of high-risk IV medications and may help prevent MEs caused by inaccurate compounding.
Administration (n=24 studies)	Smart pumps reduce, but do not completely prevent, pump programming errors. High override rates of soft limits and insufficient compliance in drug library use limit the effectiveness. Hard limits play the main role in intercepting errors. Opportunities for improvement include integrating smart pumps with barcode readers and CPOE real-time clinical data (e.g., glucose control, respiratory monitoring). Smart pumps allowing automated relays of vasoactive infusion pumps reduce hemodynamic incidents. Color-coded systems such as prefilled syringes, pediatric weight zones, and labels decrease time to medication administration and

	reduce pediatric MEs and wrong fluid errors in simulated emergencies. Anesthesia safety systems, including drug trays and trolleys, pre-filled syringes, color-coded labels, barcode drug verification, and administration record and safety alarms, reduce MEs and adverse outcomes. Procedural interventions can reduce the administration of incompatible drugs in intensive care with SOPs. Checklists designed with explicit step-by-step instructions are useful for detecting MEs when a care provider must perform a long series of mechanistic tasks under a high cognitive load. Standardizing high-risk medication use (e.g., validated algorithms for extravasation prevention in pediatric peripheral chemotherapy) can enhance patient safety by establishing rapid intervention and proper follow-up. The use of CPOE-generated orders for continuous infusions saved nurses' time and improved user satisfaction but did not decrease the incidence of MEs associated with verification of infusion pump settings. Barcode scanning is more feasible than two-person confirmation when verifying the use of the right drug. A calculator to convert orders to volumes and administration rates improved nurses' performance in drug calculations during simulated clinical scenarios. Interventions can reduce unanticipated errors of commission in medication administration tasks when interruptions occur, but effectiveness at reducing predictable errors of detection in medication verification tasks is mixed.
Treatment monitoring (n=2 studies)	Integrating a computer-based insulin protocol into a CPOE system achieved efficient, safe, and effective glycemic control in SICU patients. The use of a CPOE set improved treatment monitoring when prescribing IV haloperidol (e.g., ECG, electrolyte monitoring) and reduced the proportion of subjects who received haloperidol >2mg/24hours.
Standardization of a high-risk medication use process (n=5 studies)	Technology (CPOE, CDSS, PCA smart pumps) and safety interventions (e.g., standardized orders, education, independent manual double-checks) decrease PCA-related MEs. The use of an easily applied intervention increased the amount of IV fluid administered to patients receiving acyclovir, a potentially nephrotoxic medication. A computerized protocol for tight glycemic control resulted in significant insulin dosing error reduction in a simulated environment, saving time and improved nurse satisfaction. A multi-factorial approach to the safe prescribing, dispensing, and administration of IV potassium reduced the potential for patient harm.

For a detailed presentation of references, please see the original Study II.

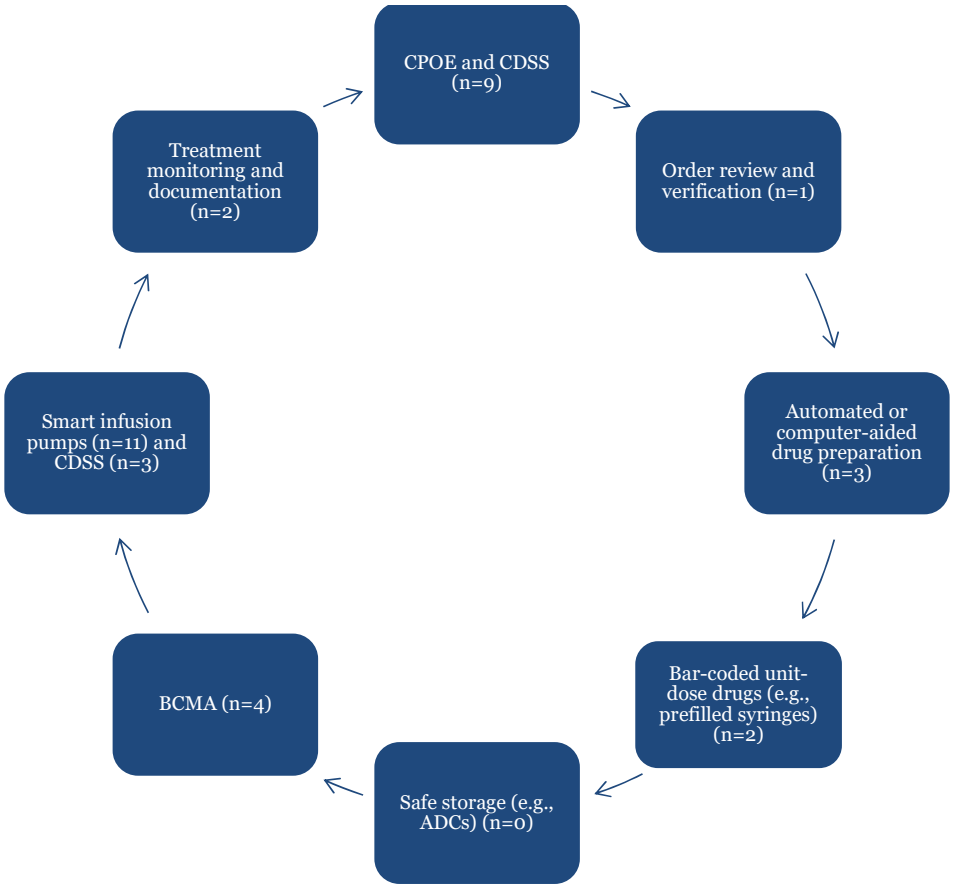

Figure 19. Systemic defenses related to closed-loop medication management explored in the included studies (n=28/46 studies, 61%) (Study II). BCMA=barcod medication administration, CPOE=computerized physician order entry, CDSS=clinical decision support system, ADC=automated dispensiong cabinet. For a detailed presentation of references, please see the original Study II.

5.2.3 UP-DATED LITERATURE SEARCH: THE MOST RECENT EVIDENCE ON SYSTEMIC DEFENSES TO PREVENT INTRAVENOUS MEDICATION ERRORS

The additional up-date search on Medline (Ovid) found 47 new articles describing systemic defenses to prevent IV MEs (Appendix 3). The studies were conducted in United States (n=16) (267–282), United Kingdom (n=7) (166,283–288), Australia (n=3) (289–291), Brazil (n=3) (292–294), Spain (n=3) (179,269,295), Mexico (n=2) (296,297), Saudi Arabia (n=2) (182,298), Singapore (n=2) (299,300), Canada (n=1) (301), China (n=1) (302), France (n=1) (303), Germany (n=1) (304), Italy (n=1) (305), Netherlands (n=1) (306), and Switzerland (n=1) (307). Some studies (n=2) were conducted in multiple countries (308,309). The studies were conducted in hospital setting (n=10)

(182,275,276,281–283,287,292,295,306), adult ICU setting (n=9) (166,269,270,272,294,296,297,308,310), hospital pharmacy setting (n=7) (267,271,277–280,309), PICU setting (n=5) (179,285,286,291,293), pediatric hospital setting (n=3) (274,284,290), emergency department (n=2) (289,300), anesthesia setting (n=1) (303), cancer hospital setting (n=1) (302), and pediatric emergency department (n=1) (298). Some studies (n= 8) were conducted in simulated environments, such as anesthesia setting (n=2) (299,304), hospital setting (n=2) (268,288), ICU (n=1) (301), NICU (n=1) (305), operating room (n=1) (273), and pediatric emergengy department (n=1) (307).

There was a lot of variation between the study designs and research methods. The designs used in more than one study were observational simulation studies (n=8) (268,273,288,299,301,304,305,307), retrospective analysis of drug preparation reports (n=6) (267,271,277,279,280,309), mixed-methods studies (n=5) (166,283,284,286,295), observational studies (n=5) (269,270,276,278,298), retrospective analysis of smart infusion pump alert log data (n=5) (179,182,275,282,297), studies measuring costs or cost effectiveness (n=4) (287,293,303,306), observational intervention studies (n=3) (281,290,292), retrospective or observational studies measuring drug consumption (n=2) (272,296), chart reviews (n=2) (289,291), and studies to design and develop systemic defenses (n=2) (285,308). Other methods included analysis of administration error reports (n=1) (274), survey study (n=1) (300), implementation of healthcare failure mode and effects analysis (HFMEA) (n=1) (302), a systematic review (n=1) (310), and a systematic review with meta-analysis (n=1) (294).

Some themes related to systemic defenses to prevent IV MEs appeared in more than one study, and these included smart infusion pumps with DERS (n=8) (179,182,275,283,293,294,296,297), IV preparation workflow softwares (n=5) (267,271,277,279,309), ready-to-use IV injections and infusions (n=5) (268,276,284,303,306), applications to help drug dose calculations (n=4) (298,304,307,308), standard concentrations of IV infusions (n=4) (285,286,291,295), IV preparation robotic systems (n=2) (280,305), smart infusion pump interoperability with EHR (n=2) (166,282), and user-tested injectable medicines guidelines (n=2) (287,288). In addition, five studies explored implementation of multiple systemic defenses to prevent IV MEs (272,274,281,301,302). Other systemic defense categories (n=10) included dose-banding for pediatric IV infusions (n=1) (290), dosage flow restrictor device for IV syringes (n=1) (300), IV administration port allowing injection only after barcode verification (n=1) (299), IV Y-site compatibility table (n=1) (310), peripheral IV drug protocol to avoid central venous catheter (CVC) insertion (n=1) (269), pharmacist's order verification (n=1) (292), redesigned infusion labels (n=1) (273), remote sterile product pharmacist checks (n=1) (278), structured IV infusion orders (n=1) (289), and structured titration instructions for continuous infusions (n=1) (270).

5.3 OPTIMISING THE DOSING LIMITS IN NEONATAL INTENSIVE CARE UNIT'S (NICU) INFUSION PUMP DRUG LIBRARY PRIOR TO IMPLEMENTATION (III)

5.3.1 QUANTITATIVE ANALYSIS OF MEDICATION ERROR REPORTS (PART 1A)

Altogether, 601 ME reports were submitted in HUS NICU during 2018–2019. Of all NICU ME reports, 3.5% (n=21/601) involved an error or near-miss related to the wrong infusion rate. Characteristics of these ME reports are described in Table 18. Over half of the ME reports (n=13/21) involved ISMP high-alert medications (n=15), comprising fentanyl (n=3), norepinephrine (n=3), insulin (n=3), parenteral nutrition (n=2), heparin (n=2), milrinone (n=1), and dopamine (n=1).

Table 18. *Characteristics of wrong infusion rate-related medication errors (MEs) (n=21) were reported at the neonatal intensive care unit (NICU). Only classes occurring in the ME reports are presented.*

Characteristic	Class	n (%)
Error nature	Medication error	20 (95%)
	Near-miss	1 (5%)
Error type	Administration error	16 (76%)
	Prescribing error	4 (19%)
	Documenting error	1 (5%)
Harm to patient	Moderate harm	2 (10%)
	Minor harm	14 (66%)
	No harm	3 (14%)
	Not reported	2 (10%)
Harm to the unit	Additional work or minor procedures	20 (95%)*
	Additional costs	2 (10%)*
Risk classification**	Moderate risk (III)	15 (71%)
	Minor risk (II)	6 (29%)

* One ME report was classified into two different classes/categories.
** Risk classification is determined in the organization's incident reporting system (HaiPro) on a scale of I to V according to the severity of the injury and the likelihood of error recurrence.

5.3.2 QUALITATIVE ANALYSIS ON MEDICATION ERROR REPORTS (PART 1B)

An error mechanism was identified in more than half of the cases (n=11/21) (Figure 20). These mechanisms were categorized based on data in six classes: a decimal error in ordering (n=3), a decimal error in infusion pump

programming (n=3), mix-ups between two infusion rates (n=2), a mix-up between dose (mg) and infusion rate (mL/h) of an intermittent infusion (n=1), pausing the wrong infusion (n=1) and a communication error related to dose change (n=1). In the remaining ME reports (n=10), the open narrative did not contain a sufficient case description, which is why the error mechanism could not be identified. In most cases (n=15/21), the MEs led to an overdose, of which the largest deviation from the intended dose was 12-fold. Of the identified decimal errors (n=6), 5 led to 10-fold infusion rate (e.g., norepinephrine infusion prescribed 0.03 mL/h, but the pump programmed 0.3 mL/h) and one led to 0.1-fold infusion rate.

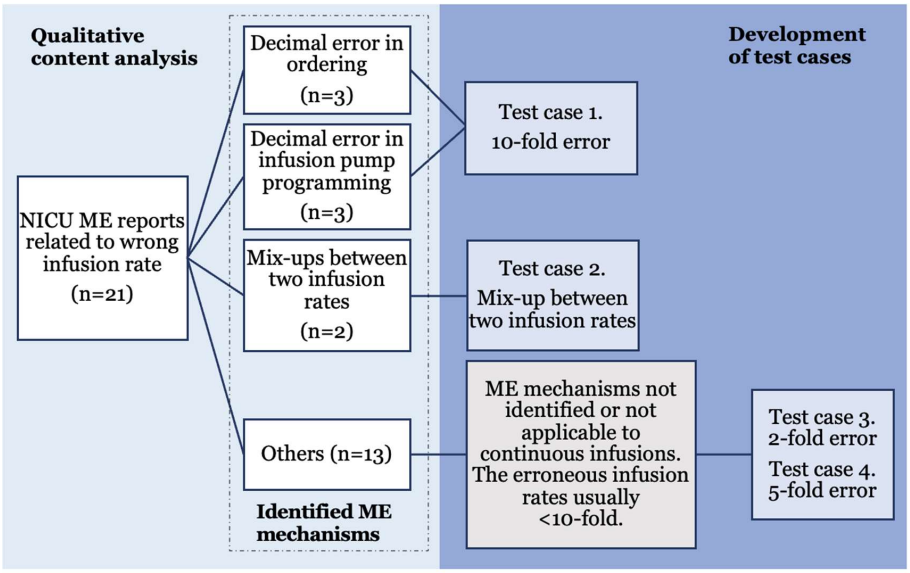

Figure 20. Development of medication error (ME) containing test cases (1-4) for simulating infusion pump programming errors. The cases were invented based on ME mechanisms identified in neonatal intensive care unit's (NICU) ME reports (n=21).

One or more contributing factors were identified in the qualitative analysis in almost all ME report narratives (n=19/21), and they were classified into seven categories based on the data. The contributing factors were failures to double-check the infusion rate (n=9), heavy workload (n=8), communication problems (n=4), interrupted drug administration (n=4), the limited number of nurses authorized to administer IV drugs (n=3), night shift (n=3), and missing systemic defenses related to ordering stage (e.g., order verification or dose-range checking in the clinical decision support system) (n=3).

5.3.3 DEVELOPMENT OF TEST CASES AND DOSING LIMITS (PART 2)

The test cases developed based on the error mechanisms identified in Part 1B are presented in Figure 20. Most of the identified error mechanisms (n=8/11)

applied to the test cases on continuous infusions, resulting in test cases 1 (10-fold error) and 2 (mix-up between two infusion rates). Some of the error mechanisms (n=3) did not apply to continuous infusions. In some ME reports, the error mechanism could not be identified (n=10), resulting to the test cases 3 (2-fold error) and 4 (5-fold error) developed based on the ME reports simulating smaller deviations than 10-fold errors from the intended doses. The selected test sample of high alert medications and their standard concentrations, usual dosages, and drug library soft upper limits are presented in Table 19. Because of the wide size variation between NICU patients, the test cases were decided to be performed with two different sized imaginary test patients (1 kg and 3.5 kg).

Table 19. *Test drugs, usual dosages, and drug library soft upper limits used in the study. GA=gestational age, SC=standard concentration.*

Drug and SCs		Usual dosage	Soft upper limit
Fentanyl	5 µg/ml 10 µg/ml	0.5–1 µg/kg/h < 37 GA 0.5–2 µg/kg/h ≥ 37 GA	2.2 µg/kg/h
Norepinephrine	40 µg/ml	0.1–0.2–0.4 (≥ 0,5)* µg/kg/min	0.55 µg/kg/min
Dopamine	1 mg/ml 2 mg/ml	2–5 –10 (–15)* µg/kg/min	16.5 µg/kg/min
Heparin flush	0.6 IU/ml	0.36–0.6 IU/h	0.66 IU/h

*The rarely used highest usual doses of norepinephrine and dopamine, which directed the establishment of dosing limits, but were not used in test cases and are presented in parentheses.

5.3.4 PERFORMING TEST CASES AND QUANTITATIVE ANALYSIS OF ALERTS (PART 3)

The results of the test cases (n=226) are presented in tables 20 and 21. Two authors (SK, KK) performed each test case independently without any observed errors in the programming of test cases. As expected, there were no alerts in test cases simulating usual dosages (n=32) (Table 20). The soft upper limits caused an alert in 73% (n=70/96) of test cases containing 2-fold, 5-fold, and 10-fold errors. The 10-fold errors caused an alert in all test cases (n=32). In the case of 2-fold and 5-fold errors, some of the lowest usual dosages did not cause an alert, as they were smaller than the maximum dosages. In the case of heparin flush having a weight-independent fixed dose, all error scenarios produced an alert. The test case regarding the mix-ups between two infusion rates (Table 21) was simulated by programming the pump with all other test drugs' rates (Table 20). The higher standard concentrations of fentanyl and dopamine were cross-programmed with each other, as they are often simultaneously used with fluid-restricted patients. The mix-ups caused an alert in 24% (n=24/98) of test cases when the erroneous infusion rate was higher than the usual maximum dose (Table 21). The remaining mix-ups did not cause an alert because the erroneous dose was lower than the usual maximum dose.

Table 20. *The results of test cases when programming the pumps with the rate corresponding to the usual dose (n=32) and erroneously with 10-fold, 5-fold, and 2-fold infusion rates (n=96). (*) identifies the test cases where the soft upper limit triggered an alert (n=70/96, 73%).*

	Patient 1.0 kg			**Patient 3.5 kg**		
Fentanyl 5 µg/ml	**0.5 µg/kg/h**	**1 µg/kg/h**	**2 µg/kg/h**	**0.5 µg/kg/h**	**1 µg/kg/h**	**2 µg/kg/h**
Soft upper limit (mL/h)	**0.44**	**0.44**	**0.44**	**1.54**	**1.54**	**1.54**
Usual rate (mL/h)	0.1	0.2	0.4	0.35	0.7	1.4
10-fold rate (mL/h)	1.0*	2.0*	4.0*	3.5*	7.0*	14.0*
5-fold rate (mL/h)	0.5*	1.0*	2.0*	1.75*	3.5*	7.0*
2-fold rate (mL/h)	0.2	0.4	0.8*	0.7	1.4	2.8*
Fentanyl 10 µg/ml	**0.5 µg/kg/h**	**1 µg/kg/h**	**2 µg/kg/h**	**0.5 µg/kg/h**	**1 µg/kg/h**	**2 µg/kg/h**
Soft upper limit (mL/h)	**0.22**	**0.22**	**0.22**	**0.77**	**0.77**	**0.77**
Usual rate (mL/h)	0.05	0.1	0.2	0.18	0.35	0.7
10-fold rate (mL/h)	0.5*	1.0*	2.0*	1.8*	3.5*	7.0*
5-fold rate (mL/h)	0.25*	0.5*	1.0*	0.9*	1.75*	3.5*
2-fold rate (mL/h)	0.1	0.2	0.4*	0.36	0.7	1.4*
Dopamine 1 mg/ml	**2 µg/kg/min**	**5 µg/kg/min**	**10 µg/kg/min**	**2 µg/kg/min**	**5 µg/kg/min**	**10 µg/kg/min**
Upper soft limit (mL/h)	**0.99**	**0.99**	**0.99**	**3.46**	**3.46**	**3.46**
Usual rate (mL/h)	0.12	0.3	0.6	0.42	1.05	2.1
10-fold rate (mL/h)	1.2*	3.0*	6.0*	4.2*	10.5*	21.0*
5-fold rate (mL/h)	0.6	1.5*	3.0*	2.1	5.25*	10.5*
2-fold rate (mL/h)	0.24	0.6	1.2*	0.84	2.1	4.2*

Dopamine 2 mg/ml	**2 µg/kg/min**	**5 µg/kg/min**	**10 µg/kg/min**	**2 µg/kg/min**	**5 µg/kg/min**	**10 µg/kg/min**
Upper soft limit (mL/h)	**0.49**	**0.49**	**0.49**	**1.73**	**1.73**	**1.73**
Usual rate (mL/h)	0.06	0.15	0.3	0.21	0.53	1.05
10-fold rate (mL/h)	0.6*	1.5*	3.0*	2.1*	5.3*	10.5*
5-fold rate (mL/h)	0.3	0.75*	1.5*	1.05	2.65*	5.25*
2-fold rate (mL/h)	0.12	0.3	0.6*	0.42	1.06	2.1*
Norepinephrine 40 µg/ml	**0.1 µg/kg/min**	**0.2 µg/kg/min**	**0.4 µg/kg/min**	**0.1 µg/kg/min**	**0.2 µg/kg/min**	**0.4 µg/kg/min**
Upper soft limit (mL/h)	**0.82**	**0.82**	**0.82**	**2.89**	**2.89**	**2.89**
Usual rate (mL/h)	0.15	0.3	0.6	0.53	1.05	2.1
10-fold rate (mL/h)	1.5*	3.0*	6.0*	5.3*	10.5*	21.0*
5-fold rate (mL/h)	0.75	1.5*	3.0*	2.65	5.25*	10.5*
2-fold rate (mL/h)	0.3	0.6	1.2*	1.06	2.1	4.2*
Heparin flush 0,6 IU/ml	**0.36 IU/h**	**0.6 IU/h**				
Upper soft limit (mL/h)	**1.11**	**1.11**				
Usual rate (mL/h)	0.6	1.0				
10-fold rate (mL/h)	6.0*	10.0*				
5-fold rate (mL/h)	3.0*	5.0*				
2-fold rate (mL/h)	1.2*	2.0*				

Table 21. *The results of mix-up test-cases when programming the pumps with another drug's infusion rate (n=98). Regardless of the patient's weight, heparin flush is always used in one of the two optional infusion rates. Therefore, only two test results are reported to mix-ups with heparin flush (N/A indicates no test result reported in the column). (*) identifies the test cases where the soft upper limit triggered an alert (n=24/98, 24%).*

	Patient 1.0 kg			**Patient 3.5 kg**		
Fentanyl 5 µg/ml	**Soft upper oft limit 0.44 mL/h**			**Soft upper limit 1.54 mL/h**		
Dopamine 1 mg/mL (mL/h)	0.12	0.3	0.6*	0.42	1.05	2.1*
Norepinephrine 40 µg/ml (mL/h)	0.15	0.3	0.6*	0.53	1.05	2.1*
Heparin flush 0.6 IU/ml* (mL/h)	0.6*	1.0*	N/A	0.6	1.0	N/A
Fentanyl 10 µg/ml	**Soft upper limit 0.22 mL/h**			**Soft upper limit 0,77mL/h**		
Dopamine 2 mg/mL (mL/h)	0.06	0.15	0.3*	0.21	0.53	1.05*
Norepinephrine 40 µg/ml (mL/h)	0.15	0.3*	0.6*	0.53	1.05*	2.1*
Heparin flush 0.6 IU/ml* (mL/h)	0.6*	1.0*	N/A	0.6	1.0*	N/A
Dopamine 1 mg/ml	**Soft upper limit 0,99 mL/h**			**Soft upper limit 3.46 mL/h**		
Fentanyl 5 µg/ml (mL/h)	0.1	0.2	0.4	0.35	0.7	1.4
Norepinephrine 40 µg/ml (mL/h)	0.15	0.3	0.6	0.53	1.05	2.1
Heparin flush 0.6 IU/ml* (mL/h)	0.6	1.0*	N/A	0.6	1.0	N/A
Dopamine 2 mg/ml	**Soft upper limit 0.49 mL/h**			**Soft upper limit 1.73 mL/h**		
Fentanyl 10 µg/ml (mL/h)	0.05	0.1	0.2	0.18	0.35	0.7
Norepinephrine 40 µg/ml (mL/h)	0.15	0.3	0.6*	0.53	1.05	2.1*
Heparin flush 0.6 IU/ml* (mL/h)	0.6*	1.0*	N/A	0.6	1.0	N/A
Norepinephrine 40 µg/ml	**Soft upper soft limit 0.82 mL/h**			**Soft upper limit 2.89 mL/h**		
Fentanyl 5 µg/ml (mL/h)	0.1	0.2	0.4	0.35	0.7	1.4
Dopamine 1 mg/mL (mL/h)	0.12	0.3	0.6	0.42	1.05	2.1
Heparin flush 0.6 IU/ml (mL/h)	0.6	1.0*	N/A	0.6	1.0	N/A
Heparin flush 0.6 IU/ml	**Soft upper soft limit 1.1 mL/h**			**Soft upper soft limit 1.1 mL/h**		
Fentanyl 5 µg/ml (mL/h)	0.1	0.2	0.4	0.35	0.7	1.4*
Dopamine 1 mg/mL (mL/h)	0.12	0.3	0.6	0.42	1.05	2.1*
Norepinephrine 40 µg/ml (mL/h)	0.15	0.3	0.6	0.53	1.05	2.1*

6 DISCUSSION

6.1 SYSTEMIC CAUSES OF INTRAVENOUS MEDICATION ERRORS (I)

6.1.1 STUDY I

The systematic review summarizing systemic causes of IV MEs in hospitals found a limited number of articles, all of them being observational studies not providing the most rigorous evidence. Current IV medication use processes remain vulnerable, which can result in patient harm. According to the included studies, administration, prescribing, and preparation are the process phases most prone to MEs. 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, ISMP recommends layering numerous strategies throughout the medication use process, standardizing the ordering, storage, preparation, and administration of high-alert medications, and improving access to information about these drugs (11,81,88). Furthermore, healthcare organizations should use multidisciplinary teams to review more carefully and standardize the use processes of high-alert medications. In addition to reactive strategies (e.g., root cause analysis of reported MEs), proactive risk management actions, such as FMEA and medication safety self-assessments, should be utilized (7,15,18,81,158,204). It is also important to include IV medications in organizational high-alert medication lists. However, they are not used in all care areas, and the consumption may not be as high as with drugs administered to other routes (11,39–41,131).

Calculation tasks were identified as a cause of wrong dose errors in multiple medication use process stages (203–205). Pediatric populations, especially neonates, are at the highest risk for life-threatening calculation errors because of weight-based dosing and the lack of adequate commercial products (26,136,140,144,158,311,312). Standard concentration procedures are important for improving IV medication safety in all patient groups (8,175,176,285,286,291,295). Calculation tasks can also be eliminated or secured by successfully implementing other systemic defenses, such as smart infusion pumps utilizing DERS, dose conversion charts, and decision support systems (8,15,88,140,311,313). In addition, smart infusion pumps can reduce MEs related to manual pump programming, which was identified as a particular high-risk task (8,88,158,161,162,167,204).

Manual double-checks are widely used in error identification, but the frequently poor quality of these procedures can enable MEs

(11,28,90,208,311,314). Examples of concerns related to these procedures include failures to complete double-checks independently, relying on accuracy and awareness of an individual, and procedures lacking sensitivity to all potential error types (90,208,315). A recent systematic review by Koyama et al. (2020) found no evidence that double versus single checking of drug administration is associated with lower administration errors or reduced harm rates (314). A large observational study by Westbrook et al. (2021) found high compliance with mandated double-checking, but the independent completion of the procedure was extremely rare (315). Even though primed double-checking was highly prevalent, it conferred no benefit in reducing errors or severity compared with single checking.

Some manual double-checks could relatively simply be replaced with more reliable technological solutions (e.g., barcode scanning during drug preparation and administration) (15,35,119,140). However, these work systems still require adaptations to policies and technology to reach better usability and utilization to secure safe medication practices (316). It is also important to implement strategies eliminating the error-prone process steps requiring double-checking procedures (e.g., reducing preparation errors by using pre-prepared syringes or sealed systems requiring minimal manipulation before use) (35,82,175,176).

The absence of a standardized order review protocol was identified as a risk factor for inheriting prescribing errors in later process stages (90,206). To support safe prescribing, an order review by a clinical pharmacist combined with CDSS would be an optimal strategy for error reduction (11,15,75,140,206,313,317,318). In addition, confusion between LASA medications can be particularly significant when high-alert medications are involved (11,15,75,132,133). Use system defenses such as Tall Man lettering (e.g., morphine and HYDROmorphone), safe storage, auxiliary labels, and barcode medication administration systems should be considered to decrease errors related to LASA medications (11,15,42,132,133,140).

6.1.2 THE MOST RECENT EVIDENCE (FROM 2016 TO OCTOBER 2021)

The up-date search demonstrated that the most recent research focuses on identifying ME risk factors related to implementing and using certain systemic defenses identified in Study II, such as smart infusion pumps (94,211,212) and IV workflow systems (210). The evolution of the IV medication use process and implementation of new technology create unexpected risks. Consequently, in addition to the benefits, the safety risks associated with using and optimizing these defenses have also been highlighted elsewhere in the literature recently (8,15,35,167).

Development from reactive methods towards proactive risk management was also observed, since prospective methods, such as failure mode and effects analysis (FMEA) (210) and inductive preliminary hazard analysis (PHA) (219) were increasingly used. It is noteworthy that new technologies, such as smart

pumps introduce new types of MEs that might have not been considered, for example, in the classifications used within current ME reporting systems (211). A study by Furniss et al. (2018) found a wide variation in procedural and documentation requirements between different organizations, resulting in variable deviation rates when deviations from these standards were measured. This data emphasizes the need for clearer evidence-based standardization and local procedures that are practical to address these issues. When it comes to IV medication guidelines, user-testing seems to be worth all the effort to make the instructions practical and easy to understand (217).

6.2 SYSTEMIC DEFENSES TO PREVENT INTRAVENOUS MEDICATION ERRORS (II)

6.2.1 STUDY II

The systematic review summarizing systemic defenses and their ability to prevent IV MEs in hospitals found 46 studies involving variable systemic defenses, study designs, and evidence quality. There were two high-quality studies and six observational studies with a large magnitude of effect. Most studies applied an observational study design without large effect and did not provide the most rigorous evidence within the included articles. Over 50% of the studies focused on the administration stage, with smart infusion pumps the most widely-studied systemic defense (n=11). We found a limited number of studies exploring other stages of the medication use process; all of them were observational low or moderate-quality studies that did not provide the most rigorous evidence. Systemic defenses involving features related to closed-loop medication management systems were explored in 28 out of 46 studies.

According to our findings, smart infusion systems reduce, but do not completely prevent, pump programming errors (162,178,181,228,243,250, 254,264). High override rates of soft limits and insufficient compliance in drug library use were identified as key limitations for effectiveness (162,181,235,239,245,250,254). To make smart pumps more effective and thus prevent pump programming errors, increasing the use of hard limits in the drug libraries is important (8,162,250). Another development area is the functionality of smart pumps and drug libraries. Differences in smart pump compliance within and between hospital systems have been identified, which might be influenced by pump type and the number of drug library profiles (275). Prevention of MEs throughout the IV medication use process requires integrating smart pumps into closed-loop medication management systems, such as electronic patient records, clinical pharmacist's review of orders, automated compounding systems, barcode verification at the bedside, and real-time clinical monitoring data (3,4,8,88,161,162).

A significant error reduction was reached in one of the high-quality studies, an RCT study exploring a system designed to reduce errors in the recording and administration of drugs in anesthesia (259). The same system was also studied in another study included in our systematic review, and it involved drug trays and a drug trolley, prefilled syringes, color-coded labels, barcode drug verification, administration records, and safety alarms in supporting safe drug administration (259,260). Color-coded systems (229,233,266) and prefilled syringes (233,256) showed effectiveness in other studies by reducing errors and time to medication administration in simulated emergencies. In the future, it is important to ensure the availability of commercial barcoded prefilled syringes and ready-to-use infusions to simplify the IV drug delivery process in the clinical area (35,175,176). These are not available in many countries, and most of the IV drug preparation is carried out by nurses and pharmacists in the ward environment, where MEs are more likely to happen (28,89,200,205).

Five of the included studies (231,237,244,248,262) focused on high-risk medication process standardization. They involved systemic defenses in multiple stages of the medication use process, which is the ISMP's recommendation to support resolving medication safety issues related to high-alert medications (11,88). Another reason to study larger parts of the medication use process is to find out how different systemic defenses work together and, on the other hand, how one systemic defense can affect multiple process stages. For example, in addition to preventing prescribing errors, computerized orders and decision support systems were found to contribute to safe dispensing, administration, and treatment monitoring by preventing errors related to the interpretation of orders, calculation tasks, and treatment monitoring (225,227,231,234,240,241).

6.2.2 THE MOST RECENT EVIDENCE (FROM 2016 TO OCTOBER 2021)

The additional literature search demonstrated that the research interest in the safety of IV preparation phase has increased, while the interest related to safe prescribing and administration also remained. Smart infusion pumps were still the most widely studied systemic defense to prevent IV MEs (179,182,275,283,293,294,296,297). A new area of research was smart infusion pump interoperability with EHR (166,282), which has been identified as an important area of development also elsewhere (3,4,8,88,161). However, some studies were not found in the additional search to Medline (Ovid), which strengthens the finding related to the growing interest in EHR interoperability with smart infusion pumps (319–323) and PCA pumps (324).

Another widely studied area of systemic defenses was IV preparation workflow software (267,271,277,279,309), accompanied by even more automatic robotic preparation systems (280,305). Given the increased research related to the safety and cost-effectiveness of ready-to-use IV injections and infusions (268,276,284,303,306), manual preparation of IV

medications in wards and especially patients' bedsides might decrease in the future. These represent alternative defenses to secure safety of the preparation phase of the IV medication use process. Another interesting opening was that clinical decision support systems had evolved towards mobile applications (e.g., applications to help drug dose calculations) (298,304,307,308). Overall, it was observed that research is focused on technological solutions, their combinations, and other systemic defenses aiming to reduce or secure manual error-prone work steps within the IV medication use process.

6.3 OPTIMISING THE DOSING LIMITS IN NEONATAL INTENSIVE CARE UNIT'S (NICU) INFUSION PUMP DRUG LIBRARY PRIOR TO IMPLEMENTATION (III)

This study aimed to optimize drug library dosing limits in smart infusion pumps prior to their implementation in a NICU environment. The study was based on the systems approach to preventive medication safety risk management, stating that risks should be identified and managed proactively before they reach the patient (7,18). The findings of our study support the use of hospitals' own ME reports and the existing literature to identify risks associated with wrong infusion rates and optimize drug library dosing limits as systemic defenses before their implementation. Based on the NICU ME reports, we developed test cases to assess the dosing limits in the NICU infusion pump drug library; the test cases may also apply to other pediatric populations. However, the reliability of test cases could be developed further using prospective data collection methods, such as direct observation, focus groups, and interviews with practitioners (7,19,90,166,325). Through this approach, we could gain an even more comprehensive understanding of mechanisms of wrong infusion rate errors within the human factors framework. Our results indicate that the literature-based calculation formula developed to define the soft upper limits in pediatric intensive care settings (173) seems to be applicable in NICU settings.

Our results are promising from the perspective of the widely reported risk of alert fatigue associated with poorly defined soft limits (see Study II) (162). As expected, the usual dosages did not cause any alerts in this study, while 10-fold errors triggered an alert in all test cases. One of the key factors that made this result possible was the contribution of the neonatologist in a careful assessment of the usual maximum doses of test drugs in collaboration with the research group. Earlier studies have reported clustering of DERS alerts around specific medications and patients (e.g., fentanyl, vasopressin, and insulin in palliative care, when sedatives and analgesics have been significantly escalated) (164). Therefore, it would be useful to target similar testing activities to these particular drugs and patient groups as presented in this study.

Our analysis of the ME reports related to wrong infusion rate resulted in similar findings to earlier studies in NICU settings (26,106,128,157,158,178). Most MEs involved a high-alert medication and resulted in overdoses. MEs can be difficult to identify before reaching the patient because of varying treatment and patient-related factors, such as small drug doses and wide size variations between different patients. However, in the NICU settings, the drug library hard limits as system-based barriers have prevented administration of doses even as high as 29-fold compared to the maximum dose (7,19,164). Especially when high-alert medications are involved, MEs with this size of deviations from the intended dose expose vulnerable NICU patients to serious adverse drug events (11,26,128,155–158,164). Following earlier studies, our analysis of contributing factors to wrong infusion rate errors also revealed that failures in the use of other systemic defenses or not having them implemented could enable errors (Study I). Consequently, a combination of different preventive error reduction strategies is needed in the IV medication use process to mitigate the effects of, e.g., environmental, operational, and team-work related factors on human performance (7,19,65,88,162).

We demonstrated that errors involving doses lower than the usual maximum dose could not have been avoided using DERS (e.g., the smallest usual doses and most test cases involving a mix-up between two infusion rates). However, a bi-directional smart infusion pump interoperable with the EHR would provide a solution for even more comprehensive management of human factors contributing to pump-programming errors due to manual adjustment of infusion rate (3,4,7,8,19,88,161,165). The system would enable auto-programming of infusion parameters (e.g., infusion rate) from the EHR system to the pump, which is then verified and followed by starting the infusion by a practitioner (8). The pump also automatically sends infusion information (e.g., dose-rate, rate changes, and IV start and stop times) to the EHR system for practitioner confirmation to record this information accurately in the patient's record. However, as with smart infusion pumps, the introduction of interoperability with EHR has been associated with challenges, such as inadequate and outdated drug libraries, pump or medications not mapped with the EHR system, and inconsistency in dosing units between the drug library, EHR, and usual pump-programming practices (166).

Our results support the use of weight-based dosing limits in NICU drug libraries, which has been reported as one of the key elements of pediatric drug libraries (173,180). As a result, all the most crucial programming errors (e.g., 10-fold infusion rate) triggered an alert. The test cases related to heparin flush demonstrated that when the medication does not require weight-dependent dosing, the drug library dosing limits are much easier to set. However, it should be noted that when smart pumps are used without EHR interoperability, a patient's weight needs to be entered into the pump when programming the infusion. This process represents an additional manual step with a chance for human error (7,19).

6.4 RELIABILITY AND VALIDITY OF THE RESEARCH METHODS

6.4.1 A SYSTEMATIC REVIEW OF INTRAVENOUS MEDICATION ERROR CAUSES (I) AND SYSTEMIC DEFENSES (II)

There are some limitations to Studies I and II. The studies were conducted following the PRISMA checklist and only peer-reviewed articles were included in the analysis (190). The literature search was restricted to articles published in English; thus, studies published in other languages were excluded. The quality of selected studies was assessed using the GRADE system, which was common at the time of the study (191). Study II extracted and evaluated the statistical significance of the results presented in the included articles. However, the registration of our study protocol to the International Prospective Register of Systematic Reviews (PROSPERO) was not made. It was not as common at the time of starting the study in 2016 as it is today (326). If a similar systematic review were repeated now, it would be useful to complete PROSPERO registration before starting the data extraction. The use more in-depth quality assessment methods of the included articles, such as critical appraisal tools by Joanna Briggs Institute, would be be justified (327,328). It would also make sense to limit further studies to specific systemic defenses and stages on the medication use process, as the additional search covering only one database for a shorter period of time resulted in many relevant articles. However, this preliminary study facilitated a new medication safety research area in Finland, so the wide scope was justified. The criteria and methodologies for systematic reviews have developed and refined significantly in recent years, suggesting that the study could have also been a scoping review type of study (328). The research material of Studies I and II consisted of peer-reviewed scientific publications, so there was no need for an ethical approval or research permission.

Although IV medications are widely used in hospitals and associated with frequent and particularly serious MEs (27,30,31), the number of studies included in Study I was limited. Many excluded studies focused on incidence and types of IV MEs, with no emphasis on examining why the errors happened. We also excluded some studies focusing on multiple administration routes if the findings related to IV administration could not be reliably identified and extracted from the results. Some modifications to the error categorizations presented in Leape's classic analysis of MEs (196) must be made. We wanted to identify the most crucial systemic causes of IV MEs to inform hospital medication use process development. Because Study I objectives, none of the included articles 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 MEs (79). Especially self-reporting methods have been associated with lack of representativeness and the issue of underreporting. We also found

many variations among study objectives, designs, and measures, which is an area of development. The administration probably seems the most complex and error-prone process stage because it was widely studied. Especially the evidence related to MEs in treatment monitoring was limited. Furthermore, some important areas, such as microbiological contamination related to preparation, were not identified. This factor was not measured in any of the studies, even though it has been recognized as an area of improvement (51,53,89).

The quality of articles included in Study II was relatively low, as most (44/46) applied observational methodologies. The studies used different measures, and study designs, so quantitative analysis was not performed. Incidence of MEs was a commonly used measure, but there was variation between the error detection methods. As in Study I, none of the studies utilized more than one error detection method. Because the data was not summarized statistically, we decided to include an earlier systematic review by Ohashi et al. (2014) in the analysis. If quantitative analysis could have been performed, double-counting the articles included in our study and systematic review by Ohashi et al. (n=9) (178,181,228,235,237,239,248,250,254) would have been a more critical source of bias. Most included studies focused on the administration stage, probably because the administration is the most error-prone stage of the IV medication use process. The number of studies covering other medication use process stages was limited since the studies exploring other phases might involve multiple administration routes. For example, none of the included studies explored automated drug distribution systems, which have been indicated to improve medication safety (47,83). We had to exclude some promising articles as they appeared to be descriptive project reports and lacked a scientific study design, indicating that this research area is still under development. Therefore, our decision to study systemic defenses in all hospital environments was a good choice, as many defenses can be modified and applied in different care settings.

6.4.2 OPTIMISING THE DOSING LIMITS IN NEONATAL INTENSIVE CARE UNIT'S (NICU) INFUSION PUMP DRUG LIBRARY PRIOR TO IMPLEMENTATION (III)

There are some limitations to the Study III. First, we used self-reported ME data to create test cases simulating errors resulting in the wrong infusion rate. Self-reporting is associated with the risk of underreporting, and it is unlikely that all MEs and near-misses were documented (79,329). The number of ME reports included in qualitative content analysis remained low. We focused only on one part of the medication use process, and neonates are a limited patient group. However, we aimed to study the possible error mechanisms contributing to wrong infusion rates, specifically in NICU settings instead of error incidence. Therefore, the self-reported ME data was found useful for the purpose of this study. To improve the reliability, two researchers

independently searched ME reports meeting the inclusion criteria and verified the findings of the qualitative content analysis, followed by a careful review of the error mechanisms and test cases by the research group, neonatologist, and neonatal nurse practitioners. Nonetheless, qualitative content analysis is a researcher's subjective interpretation. Some ME reports described the incidents only briefly, so the researchers' interpretations might not entirely correspond to the actual incidents (193). The test cases should be further developed in future studies using data collected through prospective methods and other theoretical frameworks, such as focus groups and SEIPS (Systems Engineering Initiative for Patient Safety) (325,330).

Second, we only used soft upper limits even though an effective DERS should include hard and soft upper and lower dosing limits (8,162). Earlier studies have reported a high override rate of soft limits, and therefore, all alerts triggered in our study cannot be equated as averted errors in clinical situations. However, not all pump-programming errors cause significant patient harm, which was found out in our ME analysis and has also been observed elsewhere (181). Moreover, the number of medications selected to perform the test cases was relatively small, and the selection of different test drugs might have resulted in different findings. When it comes to demonstrating mix-ups between two drug infusion rates, future studies should include designs enabling a more comprehensive exploration of environmental and team-work related factors (e.g., a simulation study with full patient scenarios and multiple end-user participants) (7,19,65,195).

Study III represents a preliminary work aiming to define dosing limits before their implementation, but the true effectiveness of these limits can be reliably evaluated only after implementation. In future studies, the alert log data and drug library compliance should be studied after implementing dosing limits to confirm whether the limits have a beneficial effect on drug library compliance and soft limit alert overrides (8,162). Also, a simulation study involving patient scenarios, real care teams, and simulated care environments would be beneficial to examine the optimal use of both hard and soft limits (195). However, Study III provides NICU and possibly other settings with means for targeting optimal dosing limits, as improperly defined hard limits can prevent legitimate actions. In contrast, unsuitable soft limits can cause useless alerts (162).

Study III was evaluated by the Helsinki University Hospital Joint Authority Administration and was determined to not be human subject research. The Helsinki University Hospital Joint Authority Administration approved access to the data and confrmed that no formal ethical approval or consent was needed. The study was evaluated and carried out in accordance with the Declaration of Helsinki and the ethical principles of research with human participants and ethical review in the human sciences in Finland (331).

6.5 PRACTICAL IMPLICATIONS

This study provides health care organizations an overview about systemic causes of IV MEs and defenses to prevent these errors. Our findings suggest further focus on medication safety practices related to administration, prescribing, and preparation of IV medications. Process standardization and implementation of wisely chosen effective systemic defenses are essential to improve medication safety. However, it is necessary to be aware of the new ME risk factors posed by the changes in the medication use process. The use of new systemic defenses may involve unexpected challenges that make it difficult to implement the ideal process in daily practice (e.g., non-optimal dosing limits in the smart pump drug library may lead to alert fatigue and complete bypass of drug library use). Consequently, proactive risk management activities and systematic monitoring of both successes and challenges should be an integral part of the implementation of new technologies.

At the beginning of this study in 2016, closed-loop medication management systems and smart infusion pumps were hardly known in Finland. However, interest in these systems has been continuously growing. A national statement of closed-loop medication management in hospitals was published in 2020 (2) and many hospitals are currently planning to adopt new technologies to promote and secure medication safety. For example, some features of closed-loop medication management systems have already been introduced in HUS recently. The findings of Studies I-II have been applied in the New Children's Hospital to support the implementation of the new EHR system Apotti in 2020. The first smart pump drug library maintained by HUS Pharmacy in NICU was introduced in 2018 and expanded to the New Children's Hospital in 2021. The findings of Study III were recently applied to practice in June 2022 by introducing dosing limits in the NICU drug library. The results can be utilized in a similar way in other healthcare organizations introducing new equipment, technological solutions, EHR systems, and facilities. This study provides direction and guidelines for the future progress of the IV medication use process in Finland and other countries at the same stage of development.

Even though medication safety as part of patient safety has been a top priority in the Finnish healthcare system for last decades, the attention paid to the safety of the IV medication use process remained limited before this study. This new research area is an opening of Finnish hospitals. IV drug administration and specificities of pharmacotherapy in rarer high-risk patient groups, such as neonates, have not been sufficiently covered in the Finnish pharmacy undergraduate education. Therefore, hospital pharmacies have needed to ensure that their staff will acquire the necessary competence and skills related to this high-risk administration route in practical work. In the future, both pharmacy students and hospital pharmacists can use this dissertation to become familiar with the medication use process, systemic defenses, and typical safety risks related to the use of IV medications,

parenteral nutrition, and IV fluids in hospitals. This thesis also provides an overview of pharmacotherapy, medication use process and medication safety risks in NICU setting. In the future, it would be necessary to integrate these topics to Finnish pharmacy education.

6.6 FUTURE RESEARCH

Because of the increased use of technological solutions and closed-loop medication management systems in healthcare, there is a need to explore the resulting new types of risks in the IV medication use process. Future studies should also investigate combinations of systemic defenses and their effectiveness in error prevention in multiple stages of the IV drug delivery process. However, challenges related to the implementation of new technological solutions and medication safety risks that arise should also be examined to improve the usability of these systems. As more data is available from the medication management systems, it is essential to use this information to assess effectiveness and areas of development. In future studies employing a similar method for defining and testing the dosing limits as presented in Study III, the alert log data and drug library compliance should be studied after the drug library implementation. There is also a need for further studies to explore systemic causes of IV MEs and defenses to prevent these errors in other settings than inpatient care, because IV administration is becoming more common in ambulatory settings, such as home infusion chemotherapy, pain management and antimicrobial therapy.

7 CONCLUSIONS

- Current IV medication systems remain vulnerable to MEs and should be strengthened with appropriate systemic defenses. 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 IV MEs. Process standardization and implementation of effective systemic defenses are essential to improve medication safety.

- Most studies exploring systemic defenses to prevent IV MEs focus currently on the administration stage, with smart infusion pumps being the most widely studied systemic defense. A limited number of studies have explored other stages of the medication use process, which would represent a crucial area for future research. However, most of the systemic defenses involved features related to closed-loop medication management systems, which enable integration of several systemic defenses at different stages of the IV medication use process.

- The updated literature search of the systematic reviews (Studies I and II) for only one database found similar numbers of publications just within a short number of years, highlighting the expansion in this area of medication safety research. The evolution of the IV medication use process and the implementation of new technology create unexpected risks worth identifying proactively. It is important to monitor and improve the usability of these systems so that they are as easy to use as planned to avoid the development of shortcuts posing unnecessary medication safety risks.

- Simulation-type test cases can be applied to assess the appropriateness of dosing limits within the NICU's drug library. In developing the test cases, combining the hospital's ME data with other prospective data collection methods is recommended to understand mechanisms of wrong infusion rate errors within the human factors framework. After drug library implementation, the alert log data and drug library compliance should be studied to verify the suitability of dosing limits. However, when the lowest usual drug doses are used, a larger deviation from the intended infusion rate is required to generate an alert. Consequently, combining smart infusion pumps to other systemic defenses in the IV medication use process is required for a more comprehensive preventive risk management approach.

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APPENDIXES

Appendix 1. Studies describing smart pumps and dose error reduction software (DERS) use in hospital settings treating neonatal patients.

Reference, country, and setting	Development of dosing limits	Study design and pump model used	Study objectives	Main measures	Results
Studies conducted in neonatal intensive care (NICU) settings					
Melton et al. 2019 (164) A level four NICU with 59 registered beds and an average of 725 yearly admissions	The drug library was customized in 2013 through an interprofessional collaborative effort. Drug library and medication issues were reviewed monthly by the team to assess medication additions and adequacy of dosing limits. Changes have been tracked since 2014, with updates occurring	A retrospective evaluation of smart pump data for all neonatal patients from January 2014–December 2016. Alaris™ (Becton, Dickinson, and Company, Franklin Lakes, NJ) intravenous infusion smart	To assess whether smart pumps effectively reduce medication errors in the neonatal population and determine whether they are a source of alert burden and alert fatigue in an intensive care environment.	Using smart pump records of over 370,000 infusion starts attempts to exceed preset soft and hard maximum limits, percent variance from those limits, pump alert frequency, patterns, and salience were evaluated.	Smart pumps prevented 160 attempts to exceed the maximum hard limit for doses as high as 7–29 times the maximum dose. They resulted in the reprogramming or cancellation of 2093 infusions after soft maximum alerts. While the overall alert burden from smart pumps for continuous infusions was not high, alerts clustered around specific patients and medications. A small portion (17%) of infusions generated the majority of alerts. Soft maximum alerts were often overridden (79%), consistent with low alert salience. Clustered alerts may generate a high alert burden and limit safety benefits by desensitizing providers to alerts. Future efforts should address ways to improve alert salience.

	on average 4–5 times/year.	pumps with DERS.			
Studies conducted in wider hospital settings treating neonates					
Larsen et al. 2005 (178) United States A 242-bed university-affiliated tertiary pediatric hospital	The task force determined the appropriate drugs and dosing ranges for the drug library. The dosing ranges were individually selected for each drug to avoid 10-fold overdoses.	Preintervention and postintervention comparison of reported medication errors related to infusion therapies between 2002 and 2003. Medex, Carlsbad, CA.	To determine if combining standard drug concentrations with "smart-pump" technology reduces reported medication-infusion errors.	Comparison of reported continuous-medication-infusion errors before and after the intervention.	The number of reported errors dropped by 73% for an absolute risk reduction of 3.1 to 0.8 per 1000 doses. Preparation errors in the pharmacy decreased from 0.66 to 0.16 per 1000 doses; the number of 10-fold errors in dosage decreased from 0.41 to 0.08 per 1000 doses. The use of standard drug concentrations, smart syringe pumps, and user-friendly labels reduces reported errors associated with continuous medication infusions. Standard drug concentrations can be chosen to allow most neonates to receive needed medications without concerns related to excess fluid administration.
Manrique-Rodríguez et al 2012 (180) Spain A pediatric intensive care	The most used PICU and pharmacy's drug information sources were identified to determine the usual doses,	An observational implementation study. Alaris® syringe pumps with Plus software.	To describe the process for developing a specific drug library for a pediatric intensive care unit (PICU) and	The development of a drug library, key factors in its design, and some of the most relevant infusion-related	Our infusion pump technology covered 108 drugs. Compliance with the drug library was 85%, and nurses' acceptance of the drug library was high as 94% would recommend implementation of this technology in other units. After nine months of implementation, several potentially harmful infusion-related

unit (PICU) with 11 beds and 500 admissions annually	maximum and minimum doses, recommended concentrations, times, and infusion rates. The calculation formula for dosing limits is presented only for intermittent infusions (1.2 x maximum dose).		the key factors for preventing programming errors.	programming errors intercepted are described.	programming errors were intercepted. Drug libraries are specifically designed for a particular hospital unit and may condition the success in implementing this technology. Implementation of smart pumps proved effective in intercepting infusion-related programming errors after nine months of implementation in a PICU. Findings related to the neonatal population could not be extracted from the results.
Manrique-Rodríguez et al. 2013 (181) Spain A pediatric intensive care unit (PICU) with 11 beds and 500 admissions annually	Not described	A prospective observational intervention study. Alaris System, CareFusion, San Diego, CA.	To estimate the patient safety benefits resulting from the implementation of smart pump technology	A systematic analysis of data stored by the devices during the designated study period (January 2010–June 2011) was conducted. The severity of intercepted errors was classified.	During the 17-month study period, the overall rate of user compliance with the safety software was 78% (486,875 of 624,252 infusions programmed through the drug library). The percentage of infusions reprogrammed after a related soft-limit alert was 30% (i.e., 70% of alerts were overridden). The use of smart pump technology resulted in the interception of 92 programming errors, 84% of which involved analgesics, anti-infectives, inotropes, and sedatives. About 97% of the errors resulted from user programming of doses or infusion rates above the hard limits defined in the

					smart pump drug library. The potential consequences of the intercepted errors were considered moderate, serious, or catastrophic in 49% of cases. Findings related to the neonatal population could not be extracted from the results.
Manrique-Rodríguez et al. 2016 (179) Spain This study investigated a tertiary level hospital pediatric intensive care unit (PICU) with 11 beds and 450 admissions annually.	In 2009 the most used PICU and pharmacy drug information sources were identified to determine maximum and minimum doses, concentrations, recommended administration times, and rates. The drug library is updated periodically (new drugs and concentrations, dosing limit modifications) to	An observational, prospective intervention study Pump model not described.	To estimate the impact of smart pump implementation in a PICU regarding the number and type of administration errors intercepted.	Users' compliance with the drug library and the number and type of errors prevented were analyzed.	Two hundred and eighty-three errors were intercepted during 62 months of study. A high-risk drug was involved in 58% of prevented errors, such as adrenergic agonists and antagonists, sedatives, analgesics, neuromuscular blockers, opioids, potassium, and insulin. Users' average compliance with the safety software was 84%. Smart pumps implementation has proven effective in intercepting high-risk drugs programming errors. Findings related to the neonatal population could not be extracted from the results.

	adapt to routine practice better. This data was first made on a trimestrial basis, and in 2013 a single annual update proved sufficient.				
Waterson et al. 2020 (182) Saudi Arabia Fifteen disciplines/ care areas across a large facility with 1852 inpatient beds and 12,601 inpatient admissions yearly	Not described	A 12-month retrospective review of drug library reports. BD Alaris System 8015LS PC Units with Guardrails 9.33 DERS software	To establish baseline data to show how metrics in the set-up and programming phase of intravenous medication administration can be produced from drug library near-miss error reports from infusion pumps.	Canceled infusions and resolutions of all infusion alerts by users were analyzed. Decision times of clinicians were calculated from the time-date stamps of the pumps' logs.	Drug library compliance was 74.29%. Wrong drug selections (LASA errors) represented 3.45% of drug library alerts and 22.40% of canceled infusions. Wrong dose selection was responsible for 2.93% of alerts and 19.08% of canceled infusions. Findings related to the pediatric or neonatal population could not be extracted from the results.

Appendix 2. Description of the studies identified in an additional search on Medline (Ovid) reporting the most recent evidence on systemic causes of intravenous (IV) medication errors (MEs) (n=16).

Reference	Country	Study design	Setting	Main results
IV preparation workflow and technology (n=3)				
Feemster et al. 2021 (210)	United States	Failure mode and effects analysis (FMEA)	Hospital pharmacy	The chemotherapy preparation workflow was defined as a 41-step process with 16 failure modes. The FMEA was useful for risk mitigation and workflow optimization prior to the implementation of an IV compounding technology.
Gilbert et al. 2018 (211)	Canada	Human factors–informed observation and analysis	Hospital pharmacy (4 sites)	Eleven latent errors possibly leading to the wrong drug or dose in chemotherapy compounding were identified. Applicable Canadian and international standards and guidelines do not explicitly address many error-prone practices.
Rashed et al. 2016 (218)	United Kingdom	Direct observation of preparation methods and concentration quantification	Pediatric hospital setting	61.5% of infusions had a morphine concentration outside 92.5–107.5 % of label strength. Sources of inaccuracy include lack of appreciation of the ampoule overfill, volumetric accuracy of different-sized syringes, and ability to perform large dilutions of small volumes.
Smart infusion pumps (n=3)				
Kirkendall et al. 2020 (211)	United States	A systematic review	Hospital setting	Smart pumps introduce their own class of medication errors. Extraction of error types and prevention

				strategies resulted in the identification of 18 error types, 21 error subtypes, and ten prevention strategies.
Marwitz et al. 2019 (212)	United States	A retrospective descriptive analysis of the infusion pump alert data	Hospital setting (17 hospital systems)	The majority of smart pump alerts generated for IV high-alert medications (HAM; 75.8%) and non-HAM (73.8%) were bypassed by clinicians, which is a symptom of alert fatigue.
Schnock et al. 2017 (94)	United States	A multisite study using the prospective point prevalence approach	Hospital setting (10 hospitals)	60% of the observed infusions were associated with one or more administration errors. Identified errors (e.g., labeling errors, bypassing the smart pump and the drug library) were predominantly associated with violations of hospital policy.
IV compatibility (n=2)				
Fernández-Peña et al. 2021 (223)	Spain	An analysis of IV compatibility data in the literature	Neonatal intensive care unit (NICU) (9 units)	Among 1945 drug combinations analyzed, 14.6% were compatible, 21.6% were potentially compatible, 11.1% were incompatible, 7.1% were controversial, and for 45.6%, there was no data. There is a gap in knowledge about a great number of NICU drug combinations.
Maison et al. 2019 (220)	France	An observational prospective survey study	Intensive care unit (ICU) and hematology sterile unit (HSU)	Drug incompatibilities accounted for 12% and 17% of drug pairs infused in the ICU and the HSU. Administration of incompatible IV drugs in critically ill patients is frequent.
Preparation and administration of IV push doses (n=2)				
Cole et al. 2019 (209)	United States	A structured chart and video review	Emergency department	Human error (19% of patients) and adverse hemodynamic events (39% of patients) were common during phenylephrine or epinephrine IV push doses.

Hfaiedh et al. 2017 (219)	France	An inductive preliminary hazard analysis (PHA)	Pediatric hospital setting	Thirty-four hazardous situations were identified, among 17 were quoted as critical and drawn 69 risk scenarios. After follow-up actions, the scenarios with unacceptable risk declined from 17.4% to 0%, and these with acceptable under control from 46.4% to 43.5%.
Errors throughout the IV medication use process (n=2)				
Wolf 2016 (213)	United States	A retrospective analysis of medication error reports	Hospital setting	Patterns in error accounts reflected cultural changes in health care organizations. Equipment, labeling, incorrect route of administration, types of errors, patient outcomes, and causal agents represented major causes of errors.
IV fluid prescribing (n=1)				
Conn et al. 2017 (214)	United Kingdom	A mixed-methods observational study analyzing critical incident reports	Pediatric hospital setting	Principal error types were incorrect rate of fluids, inappropriate choice of solution, and incorrect completion of orders. Contributing factors included complex patients, interactions with other practitioners and teams, and challenging work environments.
IV medication guidelines (n=1)				
Jones, Clarke, et al. 2021 (217)	United Kingdom	An observational human reliability analysis (HRA)	A simulated pediatric medical facility.	Discrepancies during the use of an online injectable medicines guideline were often associated with administration errors. This finding highlights the need to test the usability of guidelines before clinical use.
Postoperative patient controlled analgecia (PCA) (n=1)				
Lee et al. 2019 (222)	South Korea	A retrospective descriptive study from medical records	Hospital setting	PCA errors occurred in 0.9% of cases. Operator error was the most common type of error (54.7%), followed

				by device malfunction (32.3%), prescription error (12.3%), and patient error (0.7%).
Procedural and documentation deviations related to IV infusion administration (n=1)				
Furniss et al. 2018 (216)	United Kingdom	A mixed-methods study involving observations and focus groups	Hospital setting (16 hospital trusts)	Deviation rates (mean 47.9%; 9.9–100% at individual trusts) and procedural and documentation requirements varied considerably between hospital trusts. Some policies may be impractical and lack utility.
Residual volume for different IV administration sets (n=1)				
Cooper et al. 2018 (215)	United Kingdom	A non-interventional observational feasibility study	Hospital setting	74% of administration sets were not flushed. The mean residual volume of the administration sets was 13.1 mL and 16.7 mL for gravity and pump sets, which led to under-dosing. Flushing was standard practice for all infusions in only one area.

Appendix 3. Description of the studies identified in an additional search on Medline (Ovid) reporting recent evidence on systemic defenses to prevent intravenous (IV) medication errors (MEs) (n=47).

Reference	Country	Study design	Systemic defense	Setting	Main results
Smart infusion pumps with dose-error reduction software (DERS) (n=8)					
Giuliano et al. 2018 (275)	United States	A retrospective one-way analysis of variance (ANOVA) and a descriptive overview of smart pump alerts	Smart infusion pumps with dose error reduction software (DERS) (no comparison).	Hospital setting	There are differences in IV smart pump compliance both within and between hospital systems and IV smart pump type, and the number of drug library profiles may be influencing factors.
Ibarra-Perez et al. 2021 (297)	Mexico	A descriptive retrospective analysis of the smart pump alert reports	Smart infusion pumps with dose error reduction software (DERS) (no comparison)	Intensive care unit	Drug library compliance was 69.8%. Smart pumps intercepted infusion errors in 29.7% of infusions programmed using a drug library. Upper hard limit alerts accounted for 26.4% of pump reprogramming events.
Jani et al. 2020 (283)	United Kingdom	A retrospective review of medication error reports and observed errors	Smart infusion pumps with dose error reduction software (DERS) (no comparison).	Hospital setting	Smart pumps both prevent and contribute to administration errors. Using any infusion device rather than gravitational administration may have prevented 8–13% of errors. EHR-integrated pumps could have prevented 52–73% of errors.
Manrique-Rodriguez et al. 2016 (179)	Spain	A prospective, observational interventional study with analytical components	Smart infusion pumps with dose error reduction software (DERS) (no comparison)	Pediatric intensive care unit	Drug library compliance was 84%. Two hundred eighty-three errors were intercepted for 62 months. A high-risk drug was involved in 58% of prevented errors. Smart pumps implementation was proven effective in

					intercepting high-risk drugs programming errors.
Moreira et al. 2020 (294)	Brazil	A systematic review and meta-analysis.	Smart infusion pumps with dose error reduction software (DERS) (vs. conventional infusion pumps).	Intensive care unit	The insulin infusion programming error rate with conventional pumps was 10%–40.1 % and with smart pumps 0.3–14%. Meta-analysis of two studies favored smart pumps in reducing the relative risk of programming errors by 51%.
Palacios Rosas et al. 2019 (296)	Mexico	This study is a retrospective observational study with a pre-post design.	Smart infusion pumps with dose error reduction software (DERS) (vs. conventional pumps).	Intensive care unit	The implementation of smart infusion pumps allows savings by reducing the annual consumption of IV solutions measured in both units (18%) and liters (22.3%).
Silva et al. 2019 (293)	Brazil	Mathematical modeling for economic analysis to analyze cost-effectiveness.	Smart infusion pumps with dose error reduction software (DERS) (vs. conventional infusion pumps)	Pediatric intensive care unit	The infusion pump with a drug library may be the best strategy to avoid errors in IV drug administration. Although it has the lowest cost, the conventional pump also has lower effectiveness.
Waterson et al. 2020 (182)	Saudi Arabia	A 12-month retrospective review of drug library reports	Smart infusion pumps with dose error reduction software (DERS) (no comparison)	Hospital setting	Drug library compliance was 74.29%. Wrong drug selections (LASA errors) represented 3.45% of drug library alerts and 22.40% of canceled infusions. Wrong dose selection was responsible for 2.93% of alerts and 19.08% of canceled infusions.

IV preparation workflow software (n=5)					
Bucci et al. 2019 (267)	United States	A retrospective analysis of technology-assisted workflow (TAWF) error reports and manual error reports.	A gravimetric technology-assisted workflow (TAWF) system (vs. conventional preparation).	Hospital pharmacy	Gravimetric TAWF preparation of compounded sterile products (CSPs) is slower than manual volumetric preparation but can improve the error capture rate (0.47% vs. 41.48%). Staff perceived the TAWF method to be the safest and most accurate for producing CSPs.
Eckel et al. 2019 (271)	United States	This study is a retrospective analysis of technology-assisted workflow (TAWF) error reports and manual error reports.	Technology-assisted workflow (TAWF) in i.v.-room (vs. manual workflow, non-TAWF)	Hospital pharmacy	The use of TAWF in the IV room was associated with detecting 14 times more errors than the use of non-TAWF, demonstrating the different frequency of error in the results. TAWF also led to a faster preparation time with a lower cost for preparation.
Higgins et al. 2019 (277)	United States	A retrospective analysis of technology-assisted workflow (TAWF) error reports and manual error reports.	Technology-assisted workflow (TAWF) in IV room (vs. manual workflow, or non-TAWF).	Hospital pharmacy	The TAWF sites detected errors at a significantly higher rate (3.78%) compared to the non-TAWF sites (0.13%) ($p < 0.05$). The top error-reporting category for the TAWF sites was incorrect medication (71.66%). The use of TAWF may be associated with a decrease in turnaround time and a decrease in overall cost.
Lin et al. 2018 (279)	United States	This study is a retrospective analysis of the error report sample	IV workflow management system (IVWMS) using barcode scanning	Hospital pharmacy	The adoption of the IVWMS significantly reduced the amount of wasted and missing IV doses from 21.27% to 7.03%. The overall cost savings of using the system was $144,019 over

		hospital information system database.	and photographic technologies (vs. conventional method).		three months. The total number of errors detected was 1160 (1.14%) after using the IVWMS.
Terkola et al. 2017 (309)	Austria, Czech Republic, Denmark, Germany, and Switzerland	A large-scale, multicentre, multinational, retrospective study of preparation error reports.	An IV workflow software gravimetric system (no comparison).	Hospital pharmacy	The system detected and prevented errors that would not have been recognized with traditional methods. 7.89% of the antineoplastic drug doses had error levels outside the accepted tolerance range. The proportion of doses with deviations >10% ranged 0.49%–5.04% (mean 2.25%) and >20% ranged 0.21%–1.27% (mean 0.71%).
Implementation of multiple systemic defenses to prevent IV medication errors (n=5)					
Erwin et al. 2019 (272)	United States	A retrospective review dispensed drug doses.	Add 23.4% NaCl to a hospital formulary and develop a novel distribution process (no comparison).	Neurointensive care unit	There were no documented adverse events related to medication distribution and two adverse effects possibly related to medication administration. The study found the process of maintaining this medication in ADCs to be a safe and efficient method of storing and dispensing a high-alert medication.
Fell et al. 2016 (274)	United States	A retrospective review of administration error reports	Personnel, training, and systems related interventions aiming to reduce infusion errors related to investigational drugs	Pediatric hospital setting	The interventions included limiting personnel and units allowed to administer study drugs, specialized training about the protocol and study drug requirements, and better differentiation of the study drug from other similar drugs. The rate of administration errors

			(vs. before intervention)		significantly decreased following the specific study design changes.
Li et al. 2017 (302)	China	This work is a study to implement healthcare failure mode and effect analysis (HFMEA).	After healthcare failure mode and effect analysis (HFMEA) (vs. before)	Cancer hospital	A total of 5 failure modes were identified with high hazard scores, and 15 recommendations were made. After the intervention, the chemotherapy error rate decreased significantly from 2.05% to 0.17%.
Pinkney et al. 2019 (301)	Canada	An observational simulation study	Line labels/ organizers vs. smart pump vs. light-linking system (vs. current practice).	Simulated intensive care unit	Line labels/organizers improve infusion safety by augmenting visual communication along the pathway (e.g., infusion contents, access port) and organization (e.g., align bags to pumps, minimize tangles). Line labels/organizers should be applied even when using smart pumps since these pumps alone did not improve infusion identification.
Schnock et al. 2018 (281)	United States	A before-after observational study	An intervention bundle focusing on labeling and IV tubing, unauthorized medication, and drug library use (vs. no intervention bundle)	Hospital setting	An intervention component aiming to reduce labeling-not-completed errors effectively reduced targeted error rates, but other components of the intervention bundle did not show significant improvement in the targeted errors.
Ready-to-use IV injections and infusions (n=5)					
Benhamou et al. 2017 (303)	France	A budget impact analysis.	Labeled, ready-to-use, pre-filled syringes (PFS) (vs.	Anesthesia setting	The use of atropine PFS rather than CMP yielded a net one-year budget saving of €5,255,304. Medication errors outweighed

			conventional methods of syringe preparation (CMP))		other cost factors relating to CMP use (€9,425,448). Avoidance of wastage in the case of atropine CMP (prepared and unused) was a major source of savings (€1,167,323). PFS is more expensive than CMP, but its use would lead to significant savings.
Burger and Degnan 2019 (268)	United States	This study is an observational, randomized crossover simulation study.	BD Simplist (BDS) vs. Carpuject (CJ) vs. traditional vial-and-syringe process (TVSP)	Simulated hospital setting	The mean time for drug preparation was significantly shorter ($P < 0.004$) with BDS (28.7; 95% confidence interval [CI], 23.3–34.2) and CJ (28.3; 95% CI, 23.1–33.5) compared with TSVP (65.8; 95% CI, 57.7–73.9). Preparation errors were significantly reduced with BDS compared with both CJ and TVSP (1.4% vs. 77.8% vs. 73.6%; $P < 0.001$). Nurses ranked the BDS as the most preferred method.
Hertig et al. 2018 (276)	United States	A prospective, multisite, observational study	Ready-to-administer product (vs. IV push traditional practice)	Hospital setting	The ready-to-administer group demonstrated a statistically significant lower observed error rate (2.5% vs. 10.4%), suggesting that the use of this product is associated with fewer observed preparation and administration errors in the clinical setting.
Larmene-Beldt et al. 2019 (306)	Netherlands	A cost-minimization analysis utilizing a decision tree type economic model	Ready-to-administer prefilled sterilized syringes (PFSSs) produced by the hospital pharmacy (vs. conventional	Hospital setting	The use of PFSSs prepared in the hospital pharmacy yielded cost savings compared with the CPM on the ward. Cost savings were strongly influenced by decreased risk of medication errors and contamination of IV medication. Extrapolating these results

			preparation method, CPM).		nationwide indicated potential savings of >V300 million (US$342 million) if only PFSSs were used.
Rashed et al. 2019 (284)	United Kingdom	A mixed observational methods approach to establish, implement and evaluate.	Morphine in prefilled syringes (PFS) for use in pediatric nurse/patient-controlled analgesia (N/PCA) (no comparison).	Pediatric hospital setting	The time to set up a N/PCA was 3.7 ± 1.7 min, a one-third reduction compared with the previous system. The number of incidents associated with N/PCA infusions was reduced by 41.2%, and preparation errors were eliminated. Healthcare providers reported that using morphine PFS was an easier and safer system.
Applications to help IV drug dose calculations (n=4)					
AlGoraini et al. 2020 (298)	Saudi Arabia	A prospective observational study	Automated IV dosage medication calculation tool (AIVDMCT) (vs. no calculation tool)	Pediatric emergency department	The AIVDMCT was associated with a significant reduction in the interval from the time of order to the time of administration. This process increased the proportion of stat medications delivered within the 30-min target window.
Baumann et al. 2019 (304)	Germany	A randomized crossover simulation study.	A mobile application to support the dose calculation and administration of (vs. no application)	Simulated anesthesia setting	Medication errors can be effectively reduced with a mobile application supporting drug administration. In the simulation scenarios, the app was able to eliminate the occurrence of calculation errors and severe medication errors.
Hua et al. 2020 (308)	Australia, United States, Switzerland, and Greece	A clinician-centered design and development study.	A mobile application for determining IV dosage regimens of colistimethate (no comparison)	Intensive care unit	The developed application provides three major functionalities, namely (1) calculation of a loading dose, (2) calculation of a daily dose based on the renal function of the patient (including different types of renal replacement

					therapies), and (3) retrieval of historical calculation results.
Siebert et al. 2019 (307)	Switzerland	A prospective, multicentre, randomized, controlled, crossover, simulation study.	A mobile application for continuous IV infusions (vs. internationally used drug infusion table).	Simulated pediatric emergency department	Lower medication error rates with the mobile application than with the drug infusion table were observed. The inter-individual variance was reduced with the application, suggesting a benefit of its use by nurses with different experience levels.
Standard concentrations of IV infusions (n=4)					
Manrique-Rodriguez et al. 2021 (295)	Spain	A study combining modified double-round Delphi method and literature review	Standard concentrations of IV infusions to characterize their pH, osmolarity, and cytotoxic nature	Hospital setting	One hundred twelve drugs were standardized, and 307 different admixtures were assessed for pH, osmolarity, and vesicant nature. Of these, 123 admixtures (40%), had osmolarity values >600 mOsm/L, pH < 4 or > 9, or were classified as vesicants. For these, the selection of appropriate vascular access is crucial.
Cree et al. 2018 (291)	Australia	A prospective review of patient charts	Standard concentrations of IV infusions and dose error reduction software (DERS) (no comparison).	Pediatric intensive care unit	77 (84%) of patients weighed less than 10 kg. On average, there were seven infusions per patient, of which 98% adhered to standard concentrations and DERS. Standard concentrations did not have a negative impact on patients' daily fluid balance.
Perkins et al. 2017 (285)	United Kingdom	A systematic approach utilizing risk-assessment	Standard concentrations of IV infusions (no comparison)	Pediatric intensive care unit	For the majority 25 most common IV infusions, three weight bands of standard concentrations were necessary to cover the children's weight ranges. They kept within predefined fluid requirements and accuracy of delivery.

Arenas-Lopez et al. 2017 (286)	United Kingdom	A step-by-step approach to introducing standard concentration	Standard concentrations of IV infusions (no comparison).	Pediatric intensive care unit	The introduction of standard morphine concentrations was feasible and safe, with no serious errors reported (in terms of patient harm) up to 8 years post introduction.
IV preparation robotic systems (n=2)					
Amodeo et al. 2019 (305)	Italy	A simulated experimental controlled observational study	An IV robotics system (vs. manual preparation of injectable drugs)	A simulated neonatal intensive care unit	The median error observed during reconstitution, dilution, and final therapy of the drugs prepared by the IV robotics ranged within ±5% accuracy, with narrower ranges of error compared to manual preparation. The IV robotics consumed fewer materials, reduced costs, decreased preparation time, and optimized the medication process.
Pang et al. 2021 (280)	United States	A retrospective analysis of preparation reports from the IV preparation system's internal database.	An IV gravimetric technology-assisted workflow (TAWF) platform vs. IV robotics system	Hospital pharmacy	Implementing either an IV gravimetric TAWF system or an IV robotics system will result in similar compounding accuracy and precision. Preparation time was less with the use of the IV gravimetric TAWF vs. the IV robotic system, but the IV robotic system required less human intervention.
Smart infusion pump interoperability with electronic health record (EHR) (n=2)					
Furniss et al. 2020 (166)	United Kingdom	A sociotechnical investigation utilizing in-depth qualitative	Smart pump-EHR interoperability (no comparison)	Intensive care unit	The study reports how the system works in context, identifies contributions, and compromises patient safety with new risks that must be managed at the bedside and intensive care unit levels.

		observations and interviews.			
Wei et al. 2021 (282)	United States	Retrospective analysis of infusion pump log data	Smart pump-EHR interoperability (vs. smart pumps)	Hospital setting	Pump-EHR interoperability leads to safer administration of IV medications based on improved drug library compliance (73.8% vs. 82.9%) and more accurate smart pump programming (infusions generating alerts 3.5% vs. 2.6%).
User-tested injectable medicines guidelines (n=2)					
Jones, Franklin, et al. 2021 (287)	United Kingdom	A cost and cost-effectiveness study	User-tested Injectable Medicines Guidelines (IMG) (no comparison).	Hospital setting	User-testing of injectable medicines guidelines is a low-cost intervention that is highly likely to be cost-effective, especially for high-risk medicines.
Jones, McGrogan, et al. 2021b (288)	United Kingdom	The single-blind, randomized parallel-group in situ observational simulation study.	Injectable Medicines Guide (IMG) (vs. an IMG version revised with user-testing).	A simulated hospital setting	User-testing injectable medicines guidelines reduce the number of errors and the time taken to prepare and administer intravenous medicines while increasing staff confidence
Other systemic defenses (n=10)					
Dose-banding for pediatric IV infusions (n=1)					
Karande et al 2017 (290)	Australia	A historically controlled intervention study.	Dose-banding for pediatric antimicrobial IV infusions (vs. before intervention)	Pediatric hospital setting	Dose-banding of IV piperacillin-tazobactam (with a maximum of 15% departure from the recommended milligram-per-weight dose of 100 mg/kg) resulted in acceptable variation when compared to individualized milligram-per-weight dosing in children.

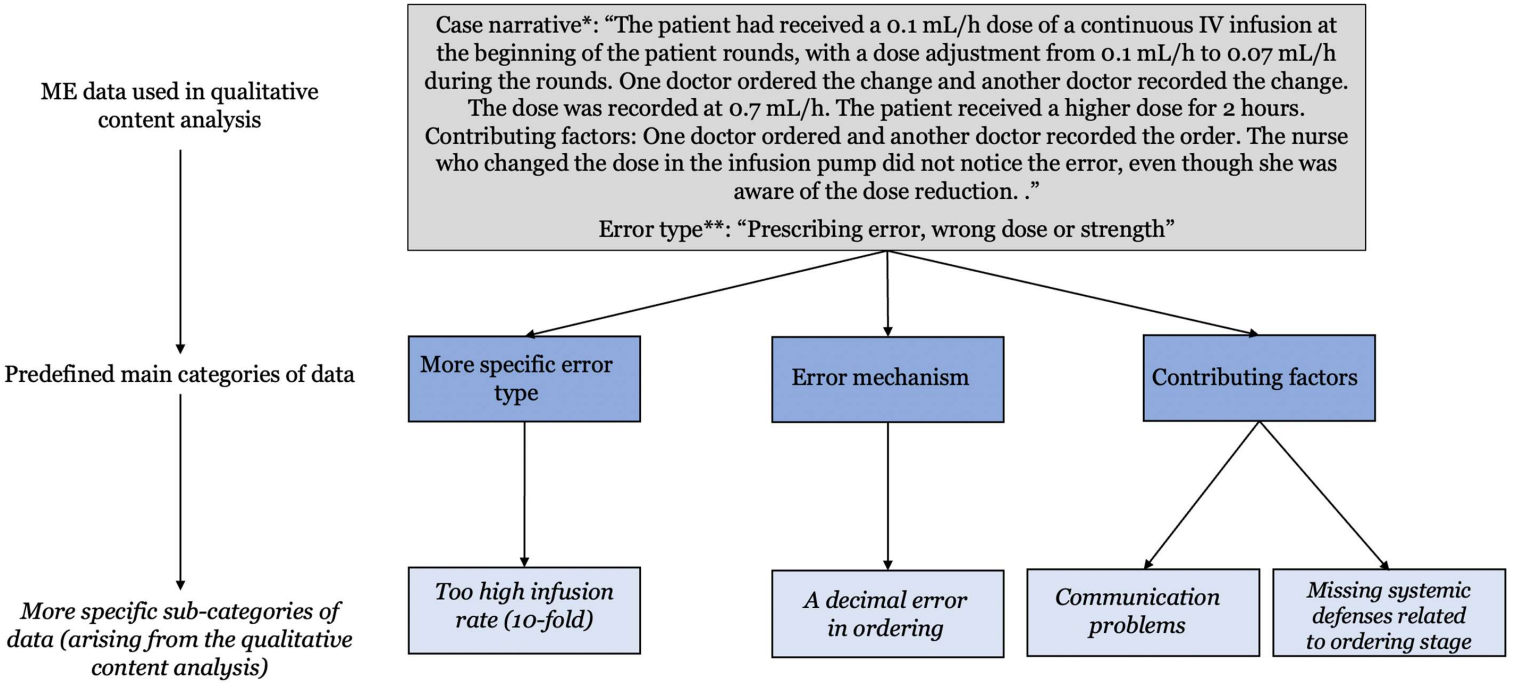
Dosage flow restrictor device for IV syringes (n=1)					
Ng et al. 2021 (300)	Singapore	A cross-sectional survey study	A dosage flow restrictor device as part of the IV morphine bolus administration workflow (no comparison)	Emergency department	Syringe Brake shows promising potential for adoption to prevent medication errors. The device serves as a constraint to prevent accidental overdose caused by user unfamiliarity or autopilot administration.
IV administration port allowing injection only after barcode verification (n=1)					
Khan et al. 2016 (299)	Singapore	A randomized, controlled observational simulation study	An IV administration port allows injection only after barcode verification of drug (vs. no device).	A simulated anesthesia setting	The use of prototype device increased safe drug administration behavior in experienced anesthetists; 33 (36.3% [95% CI 26–47%]) vs. 91 (100% [95% CI 96–100%]) in the control and intervention groups, respectively (p = 0.0001).
IV Y-site compatibility table (n=1)					
Castells Lao et al 2020 (310)	Spain	A systematic review	IV compatibility table (no comparison)	Intensive care unit	The final table shows the compatibility data of 475 out of 945 possible combinations of 2 drugs (50.3%). Of these, 366 are compatible (77.1%), 80 are incompatible (16.8%), and 29 are compatible in specific conditions (6.1%).
Peripheral IV drug protocol to avoid central venous catheter (CVC) insertion (n=1)					
Cape et al. 2020 (269)	United States	A single-center, prospective, observational pilot study.	A peripheral protocol for continuous norepinephrine IV	Medical intensive care unit	The results suggest that norepinephrine is safe to administer through a PIV at low doses for less than 24 hours using a protocol. Prevention of unnecessary central line insertion is

			infusion (no comparison).		beneficial by minimizing the risk of complications.
Pharmacist's order verification (n=1)					
Araujo et al. 2020 (292)	Brazil	A prospective, descriptive intervention study.	Pharmacist verification of inpatient IV omeprazole orders (no comparison)	Hospital setting	39.60% (n=40/101 prescriptions) of pharmacist's intervention considering inappropriate IV administration route and 44.83% (n=13/29) of interventions about the wrong diluent were accepted by the prescriber. Although partially accepted, pharmacists' interventions contributed to improved patient safety.
Redesigned infusion labels (n=1)					
Estock et al. 2018 (273)	United States	This study is a randomized controlled observational between-subjects simulation study.	Redesigned labels (vs. current commercial labels).	A simulated operating room	The redesigned labels helped participants correctly select hetastarch from the cart that was also "incorrectly stocked" with lidocaine, thus preventing some potentially catastrophic medication errors from reaching the patient.
Remote sterile product pharmacist checks (n=1)					
Jean et al. 2020 (278)	United States	This study is a multisite, double-arm, prospective observational study.	Remote sterile product pharmacist checks with a gravimetric-based technology-assisted workflow (TAWF)	Hospital pharmacy	There was no statistically significant difference in the errors detected through the remote and non-remote processes ($P = 0.177$). The median pharmacist review time in the local process was significantly lower ($P < 0.001$). Annualized cost savings of remote verification were calculated to be $23,770.08.

			system (vs. local checks)		
Structured IV infusion orders (n=1)					
Jackson and Little 2020 (289)	Australia	A retrospective chart review	Electronic N-acetyl cysteine (NAC) orders calculate the weight-based NAC volume, volume, and type of IV fluid and infusion rate (vs. manual order).	Emergency department	There were no errors in dose, the volume of IV fluid, and infusion length in the 75 (87%) cases where the electronic order was used. There were multiple errors in the 11 cases where the manual order was used. The use of the electronic order removed prescribing errors and should be considered for prescribing and administering IV NAC.
Structured titration instructions for continuous infusions (n=1)					
Chen et al. 2019 (270)	United States	A single-center, retrospective observational cohort study	Structured titration instructions on patients receiving norepinephrine (vs. pre-implementation)	Intensive care unit	Time to hemodynamic stability was significantly longer after adding norepinephrine titration instructions, even when accounting for differences in baseline characteristics.

Appendix 4. A more detailed description of the abductive content analysis in Part 1B of Study III.

Figure. An example of the abductive qualitative content analysis. ME=medication error, IV=intravenous, NICU=neonatal intensive care unit.



*The case narrative is presented in a shortened and anonymized format to ensure patient anonymity.

**Error type defined in the NICU by the persons responsible for handling the ME reports (usually a senior doctor and an assistant head nurse trained for the task according to structured HaiPro classification).

Table. Examples (n=5) of abductive qualitative content analysis of medication error (ME) reports (n=21). In addition to open case narratives, the HaiPro classification system's error type was used to support the analysis. In the first part of the analysis, the open case narratives of ME reports were searched to identify data related to predefined main categories (more specific error types, error mechanisms, and contributing factors). These findings are highlighted in yellow in the shortened and anonymized case narratives. The second part of the analysis classified the findings into more specific sub-categories arising from the data. The case narratives are presented in a shortened and anonymized format to ensure patient anonymity.

Open case narratives and classified HaiPro data used to support the abductive qualitative content analysis		**Predefined main categories of data**		
Shortened and anonymized case narrative	**Error type according to HaiPro classification**	**More specific error type**	**Error mechanism**	**Contributing factors**
		More specific sub-categories of data (arising from the qualitative content analysis)		
Continuous IV infusion started. Order 0.1 mL/h. The patient received the infusion for 25 minutes after wondering about the low infusion rate. Asked a doctor, there is an error in the order. Correct rate 1 mL/h. Contributing factors: Night shift.	Prescribing error: wrong dose or strength	*Too low infusion rate (0,1-fold)*	*A decimal error in ordering*	*Night shift*
The patient received a continuous IV infusion at 0.1 mL/h dose at the beginning of the patient rounds, adjusting from 0.1 mL/h to 0.07 mL/h during the rounds. One doctor ordered the change, and another doctor recorded the change. The dose was recorded at 0.7 mL/h. The patient received a higher dose for 2 hours. Contributing factors: One doctor ordered, and another doctor recorded the order. The nurse who changed the dose in the infusion	Prescribing error: wrong dose or strength	*Too high infusion rate (10-fold)*	*A decimal error in ordering*	*Communication problems* *Missing systemic defenses related to the ordering stage*

pump did not notice the error, even though she was aware of the dose reduction.				
A daily change of medication and fluid infusions. Patient with multiple drug infusions and an IV fluid to change. A continuous drug infusion was prescribed at a rate of 0.03 mL/h, inadvertently set to go 0.3 mL/h. The nurse who started the infusion noticed the error herself (had not yet had time to double-check the fluids). Contributing factors: There are two children in the room—lots of fluids/medications to change simultaneously, including arterial system change.	Administration error: wrong dose or strength	*Too high infusion rate (10-fold)*	*A decimal error in infusion pump programming*	*Failure to double-check the infusion rate* *Heavy workload*
The patient had the first continuous IV infusion of 0.15 mL/h and a second continuous IV infusion of 0.05 mL/h. The infusion rates were inadvertently reversed when changing the IV infusions, i.e., 1st IV infusion 0.05 mL/h and second 0.15mL/h. The patient received drug infusions at the wrong rate for two hours before noticing the situation. Contributing factors: A busy day. The patient was about to have a sterile procedure, and the infusions had to be changed before that. The infusion pump also "did the trick" and did not allow the desired rate of 0.05mL/h by always increasing the rate to 0.1mL/h, so the pump had to be replaced. Infusions could not be double-checked right away as the sterile procedure was prolonged. The nurse was also responsible for another child in the room simultaneously, which weakened concentration to this patient.	Administration error: wrong dose or strength	*Too high and too low infusion rate (3-fold)*	*A mix-up between two infusion rates*	*Failure to double-check the infusion rate* *Heavy workload* *Interrupted drug administration*

When starting an intermittent infusion, the pump was accidentally set at a rate of 20mL/h instead of the intended 4mL/h (patient's dose 20mg). This result may have been because we talked to the baby's parents simultaneously, and the focus on medication was not perfect. Because of this process, the baby received the infusion in 40 minutes instead of 60 minutes. Contributing factors: Conversation with the parents at the same time possibly interfered with concentration on the task.	Administration error: wrong method of drug administration	*Too high infusion rate (5-fold)*	*Other (a mix-up between drug dose and infusion rate)*	*Interrupted drug administration*