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Review Article

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The Clinical and Economic Burdens of Infiltration and Extravasation with Peripheral Intravenous Catheters: A Contemporary Narrative Review

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Abstract

Infiltration and extravasation are complications of peripheral intravenous catheter (PIVC) use, and some of the most common causes of catheter failure. The objective of this contemporary review is to characterize the incidence, risk factors, and clinical and economic consequences of PIVC-related infiltration and extravasation, as well as strategies for prevention. Recent evidence demonstrates that infiltration incidence ranges from 13% to 20%. Extravasation is less frequent, with a reported incidence of up to 4.5%. There are numerous patient and procedure-related factors that increase the risk of infiltration and extravasation, which are caused by the infusion of either a non-vesicant or vesicant, respectively. Infiltration is often perceived as a minor complication, but can result in skin damage (e.g., scars, blisters), infections, and nerve damage, amongst other injuries, while extravasation can occasionally lead to severe consequences such as tissue necrosis and even limb loss. Both infiltration and extravasation may require additional venipunctures, resulting in treatment delays and patient discomfort. In addition to the clinical consequences, infiltration and extravasation are associated with high economic burden. This review also highlights how different considerations should be taken based on the type of extravasations that may occur with PIVC administration of contrast media, radiopharmaceuticals, vasopressors, and chemotherapy. Ultimately, use of PIVCs requires careful risk assessment and mitigation, effective monitoring and diagnosis, and timely treatment to prevent or minimize the unnecessary burdens of infiltration and extravasation for the patient and healthcare system.

Keywords: Infiltration; Extravasation; Peripheral intravenous catheter; Economic burden; Clinical burden

Introduction

Peripheral intravenous catheters (PIVCs) are the most frequently used invasive devices in hospitals [1]. Over a billion PIVCs are inserted each year in hospitalized patients worldwide [2], and in the United States (U.S.), more than 400 million short PIVCs are inserted annually [3]. PIVCs are required for multiple purposes, including blood sampling, medication, nutrient, fluid, and blood product administration, and injection of contrast media for diagnostic imaging [4]. Even though PIVCs are an integral part of patient care, they may be inappropriately used [5,6]. A qualitative study revealed that while the rationale for inserting a PIVC is based on multiple factors, in actual practice, clinicians routinely insert PIVCs in most patients reflexively [5]. Despite attempts to standardize how and when PIVCs are used [4], the rate of catheter failure remains unacceptably high, ranging from ~19-54% across studies [7].

Some of the most common causes of PIVC failure are infiltration and extravasation (Figure 1 and Figure 2). These events can be defined as the inadvertent administration of solutions or medications into the surrounding tissue; infiltration involves a non-vesicant solution while extravasation involves a vesicant [4]. A large volume of a non-vesicant solution or medication can produce tissue damage through compartment syndrome but would not result in tissue destruction [4]. Unlike vesicants, where the damage is occurring in the surrounding tissue, irritants are capable of producing discomfort (e.g., burning, stinging) or pain because of irritation in the internal lumen of the vein with or without immediate external signs of vein inflammation [4]. Vesicants are capable of causing severe tissue injury or necrosis [4]. Common vesicants include contrast media, vasopressors, and radiopharmaceuticals [8]. Chemotherapy agents, however, can be variably classified as non-vesicants, vesicants, or irritants [9].

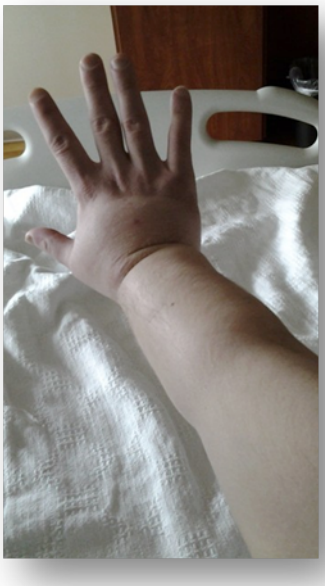

Figure 1: A large infiltration of intravenous fluid into the hand and arm of a patient who had a PIVC placed in the back of the hand. PIVC: Peripheral Intravenous Catheter.

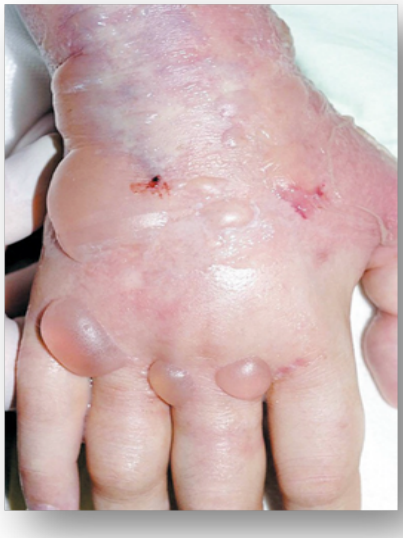

Figure 2: Extravasation of a vesicant (i.e., contrast media used for medical imaging) into the patient's hand from a PIVC that was suboptimally placed in the wrist. PIVC: Peripheral Intravenous Catheter.

In addition to the clinical consequences and harms to the patient, infiltration and extravasation can lead to significant economic burdens. A holistic review of the literature on healthcare burdens of infiltration and extravasation, as well as the epidemiology, diagnosis, and management of these events, is not yet available. Therefore, the objective of this contemporary review is to integrate the published literature to cohesively characterize PIVC-related infiltration and extravasation to help inform optimal prevention strategies.

Methods

A targeted literature review (TLR) for studies reporting on the epidemiology and burdens associated with infiltration and extravasation from PIVC use, as well as treatment and prevention strategies, was conducted using Ovid MEDLINE® (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily). As this was a TLR, only one database was searched. The search strategy was developed in collaboration with an experienced information specialist (Table 1). Predefined study eligibility criteria were used to screen all identified citations (Table 2). Example search terms included "infiltration," "extravasation," "non-vesicant," "vesicant," "irritant," "leak," "cost" and related terms (Table 1). The search was restricted to full text, published articles written in English from the last 5 years. Examples of exclusion criteria included case studies, conference abstracts, and studies focusing only on pediatrics, preclinical data, non-PIVC-associated or non-catheter-related infiltration and extravasation. A non-systematic approach was preferred to ensure an in-depth review of several targeted research questions, rather than an all-encompassing systematic review of one topic. After applying exclusion criteria and removing duplicates, the database search identified 2097 abstracts for screening. After titles and abstracts of all records identified were reviewed, ~100 full-text articles were initially reviewed, and a final 89 articles were included here. Reference lists of published reviews were screened to help supplement the list of studies included. Systematic Literature Reviews (SLRs) and/or meta-analyses, as well as narrative reviews and guidelines were selectively included based on recency of publication and relevance. Screening and data extraction were performed by one reviewer and validated by a second reviewer.

Table 1: Search Strategy

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to September 27, 2022, Search Strategy.

#	Searches	Results
1	exp "Extravasation of Diagnostic and Therapeutic Materials"/ or (extravasat$ or postextravasat$ or post-extravasat$ or ((infiltrate$ or escap$ or leak$) adj3 (vesicant$ or non-vesicants$ or nonvesicants$ or irritant? or agent? or material? or media or medium or therapeutic? or drug? or fluid? or solution? or medication?) adj5 (site? or tissue? or cavit$ or injection or injur$ or damag$ or iatrogenic or vasoconstriction? or osmotic or cytotoxic))).ti,ab,kf,kw. [EXTRAVASATION TERMS - BROAD]	22765
2	limit 1 to english language	21254
3	(Adolescent/ or exp Child/ or exp Infant/) not (exp Adult/ and (Adolescent/ or exp Child/ or exp Infant/)) [CHILDREN <19 REMOVE]	2081142
4	exp Animals/ not (exp Animals/ and Humans/) [ANIMAL STUDIES ONLY - REMOVE - MEDLINE]	5050929
5	(address or autobiography or bibliography or biography or comment or dictionary or directory or editorial or "expression of concern" or festschrift or historical article or interactive tutorial or lecture or legal case or legislation or news or newspaper article or patient education handout or personal narrative or portrait or video-audio media or webcast or (letter not (letter and randomized controlled trial))).pt. [Opinion publications - Remove -MEDLINE]	2748067
6	2 not (3 or 4 or 5) [EXTRAVASATION TERMS - BROAD - with limits]	13193
7	(ae or co or de).fs. or (safe or safety or side effect$ or undesirable effect$ or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab. [Adverse Effects Filter -SENSITIVE- Golder, Su et al. 2006 - MEDLINE]	7832393
8	6 and 7 [EXTRAVASATION & AE]	5897

9	"Extravasation of Diagnostic and Therapeutic Materials"/ep or "Extravasation of Diagnostic and Therapeutic Materials"/ mo or exp Epidemiologic Factors/ or Epidemiological Monitoring/ or Data Collection/ or Incidence/ or Prevalence/ or Databases, Factual/ or Registries/ or exp Vital Statistics/ or exp Population Surveillance/ or exp "Surveys and Questionnaires"/ or (epidemiolog$ or incidenc$ or prevalen$ or ((clinical or disease$ or factual) adj database$) or (extravasat$ adj3 database$) or register or registers or registry or registries or population statistic$ or vital statistic$ or vital registration$ or surveillance$ or ((clinical or disease$ or health) adj3 (survey$ or questionnaire$)) or (extravasat$ adj5 (survey or questionnaire$)) or (extravasat$ adj5 (comorbidit$ or co-morbidit$ or morbidit$ or multimorbid$ or multi-morbidit$ or mortalit$)) or (extravasat$ adj5 (frequency or frequencies or number or numbers or rate or rates or statistic$))).ti,kf. [EPIDEMIOLOGY TERMS - MEDLINE]	3714404
10	6 and 9 [EXTRAVASATION & EPIDEMIOLOGY]	957
11	exp "costs and cost analysis"/ or costs.tw. or cost effective$.tw. [McM Cost balanced]	521496
12	(cost$ or cost benefit analys$ or health care costs).mp. [McM Econ balanced]	835638
13	Economics/ or exp "Costs and Cost Analysis"/ or Economics, Nursing/ or Economics, Medical/ or Economics, Pharmaceutical/ or exp Economics, Hospital/ or Economics, Dental/ or exp "Fees and Charges"/ or exp Budgets/ or exp models, economic/ or markov chains/ or monte carlo method/ or exp Decision Theory/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. or ((cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or analy$ or outcome or outcomes)) or economic model$).ab,kf. or ((value adj2 (money or monetary)) or markov or monte carlo or budget$ or (decision$ adj2 (tree$ or analy$ or model$))).ti,ab,kf.	714808
14	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	356345
15	13 or 14 [CADTH Econ filter - non-validated]	852708
16	(economics/ or exp "costs and cost analysis"/ or economics, dental/ or exp "economics, hospital"/ or economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or (value adj1 money) or budget$).ti,ab.) not (((energy or oxygen) adj cost) or (metabolic adj cost) or ((energy or oxygen) adj expenditure)).ti,ab. [NHS EED Econ filter - tested for performance]	1130567
17	exp Delivery of health Care/ec or exp Hospitalization/ or exp Health Resources/ or "Facilities and Services Utilization"/ or exp Utilization Review/ or Absenteeism/ec or Presenteeism/ec or Sick Leave/ec or (((healthcare or health care or resource? or review?) adj3 (utili#ation? or utilise? or utilize? or utili#ing)) or ((length$ or duration) adj2 stay) or (number adj2 (night? or day?) adj2 stay$) or (time adj2 discharge) or ((hospital$ or primary care or surger$) adj (visit$ or contact$ or attendance$ or admission$ or episode$)) or (hospital adj2 cost$) or hospital day$ or ((patient$ or inpatient$ or in-patient$) adj (cost$ or stay)) or ((clinic? or surger$ or hospital?) adj2 (work-flow or work flow)) or (consultation$ adj2 (time or length)) or hospitalization$ or hospitalisation$ or rehospitalization$ or rehospitalisation$ or re-hospitalization$ or re-hospitalisation$ or ((patient? or inpatient$ or in-patient$) adj3 (management or care continuity or navigat$ or transfer$ or handoff or hand-off or discharge$ or transition$ or triage)) or ((absentee$ or presentee$ or productivit$ or ((work$ or employ$) adj5 (absenc$ or absent$ or presenc$ or present$)) or ((work$ or employ$) adj5 abilit$) or (time adj1 away) or ((sick or medical) adj leave)) adj8 cost?)).ti,ab,kf,kw. [HCRU TERMS]	820245
18	11 or 12 or 15 or 16 or 17 [COSTS/ECONOMICS/HCRU TERMS - combined filters - MEDLINE]	2010081
19	6 and 18 [EXTRAVASATION & COSTS/ECONOMICS/HCRU]	769
20	exp epidemiologic studies/ or odds ratio/ or exp risk/ or case-control studies/ or (random$ or cohort$ or (case$1 adj control$) or risk$ or (odds adj ratio$1) or causa$ or (relative$1 adj risk$) or predispos$).ti,ab. or (randomized controlled trial or controlled clinical trial or practice guideline).pt. [ETIOLOGY - EBM filter - MEDLINE]	6749349
21	6 and 20 [EXTRAVASATION & ETIOLOGY]	3327

22	8 or 10 or 19 or 21 [EXTRAVASATION - ALL RESULTS - BROAD]	7549
23	**limit 22 to yr="2017 -Current" [5 yrs limit]**	**2105**

Table 2: Inclusion and exclusion criteria.

PICOS	Description
Population	• Adults (≥18 years of age) • No specific disease indication
Intervention/Comparators	• Extravasation, infiltration
Outcome	• No restriction on outcomes. Interested in the following: • Distinctions between infiltration and extravasation in terms of vesicant and non-vesicants and common references to these terms in the literature • Causes of these events/complications • Epidemiology (e.g., incidence, prevalence, key risk factors) • Consequences of these complications, including pain, discomfort, other patient implications, follow-up requirements and treatments • Healthcare resource use and health economics of diagnosis and treatment of these events
Study Types	• Published, peer-reviewed studies; Exclude abstracts and posters
Exclusions	• Non-English • Articles ≥ the last 5 years • Non-human • Pediatrics • Case reports, letters, viewpoints, opinions, abstracts • Central catheters (i.e., central venous catheters, arterial catheters, peripherally inserted central catheters, wound catheters, epidural, and ports (tip is central) • Non-catheter related extravasation/infiltration

Results and Discussion

Incidence and Risk Factors

Infiltration and extravasation are well-established complications of PIVC use. Incidence rates for infiltration and various types of extravasations are presented in Table 3. A 2020 meta-analysis of 45 studies reported a pooled incidence of 13.7% for patients with either infiltration or extravasation [10]. Since more than 400 million short PIVCs are inserted annually in the U.S. [3], this would amount to approximately 56 million people with these events. This meta-analysis also found that the pooled incidence rate for these events in the Emergency Department (ED) was significantly higher than other departments (25.2%; P = 0.022) [10]. In observational studies from both European and Asian hospitals, the incidence of PIVC-related infiltration has been reported to range from 16% to 20% (Table 3) [11-14]; for extravasation, the incidence has been reported to range from <1% to 4.5% [15,16] (Table 3). The variability between studies may be largely due to differences in patient populations, the medications and solutions infused, as well as the lack of a uniform or validated standard for assessing infiltration or extravasation. It has also been postulated that rates in the literature are vastly underreported [17]. For instance, a study of PIVC failure in adults found that incidence rates for infiltration were underestimated based on clinical examination versus ultra sonographic evaluation (9.7% vs. 56.5%) [18].

The risk of infiltration and extravasation can be influenced by multiple non-modifiable and modifiable factors (Table 4). Examples of key non-modifiable patient-related risk factors include elderly patients [12,16], those who are female [14,19], and presence of comorbidities including cancer, neurological disorders, and circulatory disease [16]. While these inherent factors are challenging to control, most factors are modifiable, including indwelling site and dwell time. In general, catheter placements in areas of flexion pose higher risk and should be avoided [4,16]. Observational data show an increased risk of infiltration with the upper arm, antecubital fossa, and the forearm compared to the back of the hand [8]. While veins on the back of the hand are often easily observed, extravasation at this site can result in more severe injury [20]. However, an SLR and meta-analysis found no significant difference between the forearm and the back of the hand with respect to infiltration or extravasation [21]. Nevertheless, using the back of the hand as an insertion site should be considered in the context of multiple factors, including frequent movement leading to potential disruption of the catheter, the relatively thin and sensitive skin, limited subcutaneous tissue, and the risk of joint flexion, which can cause discomfort, complications, and catheter instability. In a Randomized Controlled Trial (RCT) of 3,050 participants involving clinically-indicated catheter removal, the incidence of infiltration from traditionally placed PIVCs was statistically significantly different between insertion sites ($P = 0.01$), with PIVCs located in the upper arm having a significantly higher incidence of infiltration (28.6%) versus the cubital fossa, hand, inner forearm, and outer forearm [22]. Ultrasound-guided PIVCs were not used in this study [22]. A 2022 SLR found that clinically-indicated replacement of PIVCs was associated with a higher risk of infiltration versus routine replacement every 72 to 96 hours [23], indicating that dwell time can be an important risk factor. Multiple insertions and clinician inexperience are additional modifiable factors consistently shown to increase the risk of infiltration and extravasation; however, there are conflicting data on whether gauge size is a risk factor for these events [11,12,19].

Infiltration rates have been shown to vary with catheter length, another modifiable factor. Most studies examined infiltration in relation to short PIVCs, which are generally inserted into superficial veins, and incidence rates reported in Table 3 largely reflect this. Two additional peripheral vascular access devices are midline catheters and Long Peripheral Catheters (LPC). Midlines are inserted into deep arm veins and terminate just inferior to the axilla, while LPCs can be inserted in either superficial or deep peripheral veins [4]. To insert LPCs, the modified Seldinger approach is commonly used, which involves using ultrasound to locate a blood vessel, followed by needle insertion under ultrasound guidance. A guide wire is then passed through the needle into the vein, providing stability for catheter placement [24]. The adjusted complication rate for infiltration from a midline catheter was reported to be 1.93% in an SLR of 7 studies across 5 countries (Table 3) [25]. For long PIVCs in hospitalized patients with difficult venous access, the unweighted incidence of infiltration was reported to be 0.9% from a smaller SLR (Table 3) [24]. While both midline catheters and long PIVCs have advantages over standard ultrasound-guided PIVCs and tend to show lower mean infiltration rates than those reported with short PIVCs, they should only be used under the appropriate clinical circumstances [24,25].

Infusate Types as Risk Factors

Infiltrated or extravasated medications or solutions are classified as 'non-vesicants,' 'irritants,' or 'vesicants' according to their potential to cause damage when infused with a PIVC [20]. According to the Infusion Therapy Standards of Practice, solutions with extremes in pH and osmolarity should be avoided to lessen vascular endothelial damage [4]. Furthermore, continuous infusion of medications with irritant or vesicant properties should be avoided and the risks and benefits of intermittently infusing vesicant medication for more than 6 days should be evaluated by increasing catheter site surveillance [4]. As the association between irritants and vesicants and the risk of infiltration or extravasation have been shown across many studies [11,12,14,19,26], it is critical for clinicians to understand the risk of these complications with the medication being infused, as infusate type is generally a non-modifiable factor. The BD Infusate Consideration Companion (ICC) provides complication/adverse event information on select, commonly used infusates (e.g., vesicants, chemical irritants, chemotherapy) to aid in vascular access device selection. Infusates are organized by drug family and are listed in tables, which include pH range and noted complications, such as phlebitis, potential damage from extravasation, recommendations on whether a peripheral infusion site should be rotated, and if a central line is preferred, amongst other vascular-access related complications/adverse events. The ICC was informed based on several hospital formulary lists, a comprehensive medication inventory database, and expert clinician guidance [27-29].

Vasopressors, commonly classified as vesicants, are often used in the treatment of patients in shock, and are ordinarily administered via large central veins to constrict blood vessels [30]. However, infusion of vasopressors through a PIVC is sometimes performed to hasten the administration of this therapy in critically ill patients [31]. Although extravasation rates related to vasopressor use have ranged across studies from 0% to 13%, most studies reported a rate less than 5% with PIVCs, including a systematic review of seven studies (Table 3) [32-36]. Risk factors for vasopressor-related extravasation are both modifiable and non-modifiable and include those related to the infusate (dose, rapid rate, high volume, prolonged or peripheral administration, saline concentration, pH, and osmolarity), procedure (e.g., catheter

type), and patient characteristics (e.g., hemodynamic instability) [17,37,38]. Of note, vascular risk factors, including hypertension, diabetes, hyperlipidemia, and coronary artery disease, have been suggested to increase likelihood of ischemic limb complications if vasopressor extravasation was to occur [39].

Chemotherapy is another important risk factor for extravasation and it is estimated that about half of all chemotherapy is infused with a PIVC in the U.S [40]. The rate of chemotherapy-related extravasation with PIVCs has been reported to range from 0% to 4.2% [40-45] (Table 3). However, in the two studies reporting 0% extravasation (Table 3), patients in fact exhibited persistent abnormalities, such as subcutaneous edema, which is an early sign of chemotherapy extravasation [44,45]. Modifiable and non-modifiable risk factors for chemotherapy extravasation from a PIVC include certain patient characteristics and anatomy (e.g., older age, small, and/or fragile veins, circulatory problems, obesity, excessive patient movement, impaired level of consciousness), procedural (e.g., size of cannula, multiple insertions, indwelling site, failure to secure the venipuncture site, untrained or inexperienced staff etc.) and product/infusion-related factors (e.g., duration and/or volume of solution, vesicants and irritants) (Table 3) [9,20,40-42,46].

Another key type of infusate-related extravasation is contrast-induced. Approximately 54 million diagnostic imaging examinations using contrast media are conducted annually in the U.S., including nearly all angiography and nearly one-half of computed tomography (CT) scans [47,48]. Radiotracers used in combination with CT or Positron Emission Tomography (PET) are another source of extravasation [49,50]. Incidence of contrast-related extravasation from PIVCs typically ranges below 1%, with incidence reported to increase to 6.7% with involvement of radiopharmaceuticals [51-58] (Table 3). A 2018 systematic review reported that using an existing PIVC that has previously been placed has higher risk of contrast extravasation than placing a new PIVC [51]. Furthermore, there is limited research into the impacts of ultrasound-guided PIVCs on contrast extravasation rates. An SLR found that ultrasound-guided PIVCs were not considered to have an impact on contrast extravasation [59], which was supported in a retrospective cohort study in the U.S., which compared ultrasound-guided placement of PIVCs versus LPCs, which are placed under combined ultrasound and wire guidance [60].

Table 3: Incidence of infiltration and extravasation from PIVCs.

Study details	Incidence	Source
Pooled infiltration/extravasation		
SLR and meta-analysis (45 studies, 76,977 catheters)	13.7%	[10]
Infiltration		
Portugese cohort study in a hospital medical clinic (n = 110)	15.8%	[11]
Serbian observational cohort study at a tertiary healthcare clinic (n = 110)	16.3%	[12]
Chinese prospective observational study (n = 1,477)	19.5%	[13]
Chinese prospective observational study at a tertiary hospital (n = 1,069)	17.8%	[14]
SLR including data from 5 countries (7 studies) for midline catheters (n = 8,783)	1.93% [a]	[25]
SLR of 6 cohort studies including data for long peripheral catheters (n = 350)	0.9%	[24]
Extravasation		
French prospective study at an infectious disease unit (n = 509)	4.5%	[15]
Chinese retrospective study at a hospital (n = 694,043) [b]	0.038% [b]	[16]
SLR of 17 studies of patients undergoing contrast-enhanced MRI or CT (n = 1,104,872)	0.2%	[51]
U.S. retrospective study of patients undergoing contrast-enhanced CT (n = 14,558)	0.34%	[53]
South Korean retrospective study of patients undergoing contrast-enhanced CT (n = 142,651)	0.23%	[52]
Taiwanese retrospective study of patients who received IV contrast media (n = 67,129)	0.04% [c]	[54]

German prospective study of patients undergoing contrast-enhanced CT (n = 3,514)	0.71%	[55]
Australian retrospective analysis of CT/PET study (n = 296)	1.3%	[57]
Study pooling PET and CT scans from U.S. and Australia (n = 863)	6.7%	[58]
A quality improvement CT/PET study (n = 5,541)	6.2%[d]	[56]
U.S. study - national benchmark rate from 11 cancer centers (739,812 infusions)	0.09%	[40]
Retrospective study at a U.S. community cancer center (12,872 infusions)	0.17%	[41]
Japanese cross-sectional observational study of patients undergoing chemotherapy (n = 12,475)	0.18%	[42]
Japanese cross-sectional observational study of patients undergoing chemotherapy (n = 24)	4.2%	[43]
Japanese prospective study of outpatient chemotherapy (n = 41)	0%	[45]
Japanese prospective study of outpatient chemotherapy (n = 63)	0%	[44]
SLR of 7 studies on complications after PIVC-infused vasopressors (n = 1,382)	3.4%	[32]
Dutch retrospective study on PIVC-infused norepinephrine (n = 14,385)	0.035%	[33]
U.S. retrospective study of long-term use of vasopressors by midlines (n = 248)	0.004%	[34]
Australian retrospective study of critically ill patients receiving vasopressors (n = 212)	13%	[35]
Rwandan prospective cohort study of critically ill patients receiving vasopressors (n = 64)	2.9%	[36]

[a]Adjusted complication rate. [b]Study includes different drugs including hypotonic or hypertonic drugs, contrast media, strong acid or alkali drugs, antineoplastic agents, inotropic agents, and other drugs. [c]Large-volume contrast media extravasation (≥20 ml) rate ((27/67,129). [d]Aggregated unadjusted infiltration rate (adjusted rate was 5.7%).

Abbreviations: CI = Confidence Interval; CT = Computed Tomography; ICU = Intensive Care Unit; NR = Not Reported; PET = Positron Emission Tomography; PIVC = Peripheral Intravenous Catheter; SLR = Systematic Literature Review; U.S. = United States.

Additional modifiable and non-modifiable risk factors that have been reported to increase risk of contrast-related extravasation, such as with CT, PET and/or MRI, have been reported to be female sex, inpatient status, older age, high injection rates, catheter location, high-density contrast, failing to warm up viscous contrast media, and indwelling site [51-53,56,59,61-63]. In reference to radiotracers, the dose absorbed into the tissues depends on the initial amount of paravenous radioactivity, the mass of infiltrated tissue, the type of radiopharmaceutical, and the length of time the extravasated product remains near the injection site [64]. The length of time is influenced by the patient's anatomy, vascular health, and injection rate [64]. Other risk factors include female sex, higher glucose levels [57], lower body weight [56], indwelling site, and flush volume [56,57,64].

Overall, a comprehensive understanding and awareness of both modifiable and non-modifiable factors (Table 4) will likely aid in more efficient diagnosis and treatment, and ultimately improve preventative efforts to reduce infiltration and extravasation from PIVCs.

Table 4: List of modifiable and non-modifiable risk factors for infiltration and extravasation.

Modifiable factors	Non-modifiable factors
Excessive patient movement [20]	Patient age [12,51]
Indwelling site [16], particularly use of the upper arm [8]	Patient sex [51]
Multiple insertions [11,20]	Patients with small and/or fragile veins [9,20]
Catheter gauge/size [9,20]	Patients with cancer, neurological-related diseases, and circulatory-related diseases [16]
Catheter dwell time [14]	Patients with communication difficulties, cognitive/function impairment, or impaired consciousness [9,16,19]
Use of power injectables and high injection rates [51]	Patient body weight [9,20]

Flush volume [56]	Hospital setting [52]
Securing the venipuncture site [9,20]	Vesicants and irritants, and solutions with extremes in pH and osmolarity [9]
Untrained or inexperienced staff [9,20]	Duration and/or volume of solution [9]
Frequency of monitoring high-risk medications [38]	Radiotracer dose [56]
Using an existing PIVC [51,52]	
Use of ultrasound-guided PIVCs [95]	
High-density/high viscosity contrast media [52]	
Abbreviations: PIVC = peripheral intravenous catheter.	

Diagnosis

Detection of infiltration or extravasation starts with patients and healthcare professionals monitoring for early symptoms or signs, which include fluid leakage around the catheter, infusion rate slowing or stopping, and issues with blood backflow. While the Infusion Therapy Standards of Practice recommends (evidence rating = IV) the use of a standardized tool or definition to assess infiltration or extravasation that is valid, reliable, and clinically feasible [4], there are currently no existing tools that meet this criteria for adult populations. However, several tools are still used despite these limitations. The extravasation assessment tool scores the severity of symptoms described above with similarities to infiltration (i.e., color, edema, pain, and skin temperature), but with additional signs/symptoms of extravasation which may include reduced mobility, skin tissue necrosis, and/or fever [20]. Previous examples exist of extravasation injuries being categorized as mild, moderate, or severe based on the drug, clinical symptoms, and extravasation volume [65,66]. The National Institute of Health's Common Terminology Criteria for Adverse Events can also be used to grade extravasation severity from painless edema (grade 1), to erythema with associated symptoms (e.g., edema, pain, induration, phlebitis) (grade 2) to severe tissue damage (e.g., ulceration or necrosis) (grade 3) or even life-threatening consequences (grade 4) or death (grade 5) [46,67]. As noted, extravasation assessment tools for adults have not been tested for validity and interrater reliability [4]. Appropriate tools need to be developed and tested so assessment of infiltration or extravasation is not based on clinical assessment alone.

Furthermore, clinical examination of signs and symptoms may not be sensitive enough to detect cases of infiltration and extravasation in earlier stages. Alternatively, the use of technologies including ultrasound may be useful for early detection of infiltration and extravasation [68]. A study of PIVC failure in adults found that 9.7% of participants presented with subcutaneous edema on clinical exam, versus 56.5% of participants based on ultra sonographic evaluation [18]. Similarly, a study of PIVC failure in children reported PIVC-associated venous changes in 73% of accessed veins with ultrasound [69]. This potential underestimation of infiltration and extravasation highlights the need for better detection in clinical practice. In addition, patient education and monitoring are important for timely detection and treatment [70].

Treatment

Timely and appropriate treatment of infiltration or extravasation can help limit adverse effects, and often depends on the type of infusate used. Inappropriate treatment of extravasation is related to more frequent skin surgery, and treatment delays are associated with serious tissue-related harms [9,42,71,72]. Thus, effective monitoring during PIVC administration is critical to provide the best care for patients.

Recommended initial treatment options for infiltration include immediately stopping IV administration and disconnecting the IV tube from the IV device, but leaving the catheter in place [4]. Nurses should then attempt to aspirate the infiltrated fluid; the catheter can then be removed [4]. Next, the physician should be notified and the affected limb should be elevated to reduce edema and promote drainage [4]. Similar first-line treatment is recommended for extravasation (including contrast, chemotherapy, and vasopressor extravasation), with the addition of administering a drug-specific antidote [4,20,66,73]. Examples

include dexrazoxane to treat anthracycline extravasation [9] and phentolamine, a vasodilator and nonselective, reversible alpha1 antagonist, to treat vasopressor extravasation [4,70,73]. Due to issues in accessing phentolamine, alternative treatment algorithms involving terbutaline injection and nitroglycerin ointment have been recommended with reasonable evidence (i.e. second-line treatment), but further research in this area is needed [4,73].

While mild and moderate events are sufficiently managed by initial nonoperative treatments, severe events generally require an additional intervention [65]. Surgical consultation is based on signs and symptoms and their progression (e.g., compartment syndrome, tissue necrosis), rather than a specific infiltration or extravasation volume threshold [4,74]. Recommended options for treatment include subcutaneous irrigation with or without hyaluronidase, open incision and irrigation, fasciotomy, and debridement [4,65,66].

Although clear benefit has not been demonstrated with thermal applications, it remains a standard supportive care (i.e., second-line treatment) [20,75]. For non-DNA-binding vesicants and vasopressors, local warming is recommended to induce vasodilation to disperse the drug and reduce accumulation in the local tissue. For DNA-binding vesicants (except vasopressors), local cooling is recommended to induce vasoconstriction and limit drug dispersion [4,20,66,73].

Beyond first-line treatment including surgery for neurovascular compromise or compartment syndrome, additional invasive treatments for IV contrast extravasation include hyaluronidase, aspiration, and irrigation with local incisions, or manual expression of extravasate with local incisions [66]. However, there is limited evidence to support and recommend these third-line interventions [66,74]. Additional anecdotal evidence includes heparin ointment dressing with cooling [76].

For more detailed information related to treatment, The Infusion Therapy Standards of Practice [4], Kim et al, 2020 [20], and documentation from the American College of Radiology Committee on Drugs and Contrast Media [66,74] are useful resources.

Clinical Burdens

Infiltration and extravasation, alone or in combination with other complications, are commonly reported causes of catheter failure and removal across studies (Table 5). A pooled analysis of seven RCTs and two prospective cohort studies from Australia found that PIVC failure due to vessel injury (which included occlusion, infiltration, or extravasation) occurred in 19% of all PIVCs [77]. As PIVC failure from infiltration and extravasation requires the insertion of a new device, this can commonly result in treatment delays for patients [78,79].

Table 5: Proportion of PIVC failures caused by infiltration or extravasation.

Study details	Sample Size	PIVC failures	Proportion of PIVC failures	Source
Australian pilot RCT comparing standard care with insertion by a vascular access specialist	(n = 138)	54% (standard care); 48% (specialists)	Caused by infiltration: 19% (standard care); 18% (specialists)	[91]
Australian prospective observational cohort study of patients receiving ED-inserted PIVCs	(n = 391)	31%	Caused by infiltration: 32%	[90]
Japanese prospective observational study of PIVC failure in medical and surgical wards	(2,442 catheter removals)	18.8%	Caused by infiltration: 41.3%	[92]
Australian prospective cohort study in medical and surgical wards	(n = 1,000)	32%	Caused by infiltration/occlusion: 14%	[79]
Australian prospective cohort study of two cancer units	(n = 200)	34.9%	Caused by infiltration/occlusion: 18.7%	[93]
Chinese prospective cohort study in adults undergoing a first-time insertion of a PIVC	(n = 5,345)	54.1%	Caused by infiltration/extravasation: 13.8%	[94]

Abbreviations: ED = Emergency Department; NR = Not Reported; PIVC = Peripheral Intravenous Catheter; RCT = Randomized Controlled Trial.

Beyond PIVC failure, the clinical consequences of infiltration from PIVCs can be extensive and include pain, bruising, skin blisters, scarring, and nerve damage [4]. In a U.S retrospective review, chemotherapy extravasation (vesicant) versus infiltration (non-vesicant) led to a significantly increased rate of short-term complications (e.g., superficial soft tissue infection, necrosis/eschar etc.) and long-term sequelae (e.g., cosmetic defects, chronic pain etc.) [8]. Thus, the consequences for extravasation may be more severe and include soft tissue injury, necrosis or eschar formation, ulceration or full-thickness wound formation, persistent numbness, skin discoloration, chronic pain, chronic disease exacerbation, cosmetic disfigurement, deep vein thrombosis, and even fatality [8,16,80]. Data from the Premier database (2013 to 2015) found that patients with versus without PIVC complications (including extravasation) showed higher rates of death (3.6% vs 0.7%; $P < 0.001$) [81].

Clinical consequences are also apparent with specific types of extravasations. While evidence generally shows that surgical intervention is rare with contrast extravasation [53,54,82], if severe contrast extravasation is left untreated, there is a risk of ischemia from venous congestion and low arterial gradient causing necrosis, serious neurovascular compromise, or even limb loss [66]. Similarly, if chemotherapy extravasation is left untreated or if treatment is delayed, blistering, peeling, sloughing of skin, tissue necrosis, and nerve and tendon damage, as well as functional and sensory impairment of the affected area, can occur [9,42,72].

Health Economic Burdens

Alongside the clinical consequences, infiltration and extravasation are both associated with a moderate economic burden, as demonstrated by evidence from the United Kingdom (U.K.), the U.S, Australia, and China. A report from the National Health Services (NHS) Resolution from the U.K., stated that claims relating to extravasation injuries between 2010 and 2021 cost the NHS £16 million, including legal fees and damages [80]. Claims data from the U.S. which compared patients with versus without PIVC complications (including extravasation) found that mean hospitalization cost was $10,895 versus $7,009 per patient using adjusted analyses of the Premier database (2013 to 2015) [81]. In addition to claims, an exploratory analysis using government websites and the literature to estimate the overall annual cost of PIVC insertion in adult Australian ED found that the annual cost of PIVC use related to occlusion/infiltration and dislodgement was estimated at $14.01 million (Australian dollars). Specific to infiltration, an observational, prospective study of 1,069 patients at a tertiary teaching hospital in China demonstrated that median medical treatment costs were 31.7, 37.9, and 52.8 CNY for Grade 1, Grade 2, and Grade 3 infiltration from PIVCs, respectively [14]. The authors state that 25.5% of patients were likely to receive PIVC replacement in the present study, which would cost 13,000 CNY. Lastly, a European economic modeling study of the risk of developing complications of IV administration of morphine, found that the cost of managing PIVC complications (IV prescription errors, phlebitis, and extravasation) was the main model driver of the results and accounted for 73% of the total costs. However, costs of extravasation alone were marginal (€0.01– €0.02 per patient) [83]. Further studies would help to inform a more holistic representation of costs related to managing infiltration and extravasation.

Infiltration and extravasation are associated with various types of healthcare resource usage, an important contributor of which is higher hospital stay. Complications resulting from catheter use can compromise patient care, potentially causing cancellations or delays, necessitating catheter replacement, or interrupting drug administration, which can increase consumption of healthcare resources [84]. For example, for those receiving treatment for infections (e.g., antibiotics), PIVC failure can result in delays and increase hospital length of stay (LOS) [85]. In an adult Australian ED from July 2019 to June 2020, clinicians spent approximately 27,383 days inserting PIVCs, including reinsertions due to complications such as occlusion and infiltration, and dislodgement, which is time that cannot be 'saved' or 'reimbursed' [86]. Data from the Premier database (2013 to 2015) suggests that PIVC complications (including extravasation) are associated with higher spending, as well as longer and more intensive care, all of which create burdens for the healthcare system and the patient. Specifically, patients with versus without PIVC complications (including extravasation) showed longer hospital LOS (adjusted mean 5.9 days vs 3.9 days, $P < 0.001$) and higher rates of being admitted to the ICU (20.4% vs 11.0%; $P < 0.001$) [81]. The economic burden associated with infiltration and extravasation necessitates investment and adoption of cost-effective technologies and protocols to help reduce overall costs (for further details, see Prevention Strategies) [82,87,88].

Prevention Strategies

Guidelines for the prevention of infiltration and extravasation (including chemotherapy) involve considerations related to insertion-related variables (i.e., equipment selection, insertion site), administration of the drug, and specific strategies for contrast extravasation [4,9,20]. For insertion-related variables, it is recommended to use an appropriately sized cannula for the anticipated flow rate and the chosen vein [66] (ideally use the smallest cannula and largest vein possible) [9], and use of a butterfly needle should be avoided [9,58,74]. Insertion technique should be meticulous, by confirming location through blood aspiration, and flushing the catheter with a test injection [74]. After insertion, it is critical to watch for blood backflow, edema, inflammation, and pain around the cannula [20]. Insertion at the level of the joints should be avoided because the catheter is difficult to secure, and

if extravasation occurs it can cause neural damage and tendon injury [20,74]. Placement of the cannula in the antecubital fossa area should also be avoided as it is extremely difficult to detect extravasation at this site [9,20,74]. While veins on the back of the hand are often easily observed, extravasation at this site can result in more severe injury [20]. Instead, veins found on the dorsal and ventral surfaces of the upper extremities, including the metacarpal, cephalic, basilic, and median veins are preferred for both short and long PIVCs, while the upper arm site is preferred for midline catheters [4]. Lastly, ultrasound-guidance to ensure the quantity of catheter residing within the vein may help with prevention of catheter failure. A study of adult emergency department patients with ultrasound-guided IVs showed that optimum catheter survival occurs when ≥65% (or two-thirds) versus when < 30% (or one-third) of the catheter resides in the vein, which is highly correlated with the hazard of failure within 72 hours [89].

In addition to insertion site and catheter gauge, staff are required to have knowledge of drug characteristics, comply with manufacturer recommendations, and educate patients on risks associated with PIVC administration [9]. When administering the drug, the catheter should be secured but not covered with opaque gauze (which would obstruct observation) [9,20]. Vesicant drugs should be administered by a new IV route; if there is an existing IV route, it is recommended to re-insert the PIVC for drug administration [20]. If possible, stimulant drugs should be diluted and administered at an appropriate rate.

Lastly, based on risk factors, there are specific recommendations for additional preventative and minimization measures related to contrast extravasation [66]. Grade B recommendations (Consistent level 2 or 3 studies or extrapolations from level 1 studies) include: 1) warming contrast medium, especially for more viscous fluids [52]; 2) minimizing the injected contrast medium based on the indication and patient size [66]; 3) using the catheter-appropriate pressure and flow rates [66]; and 4) having effective detection protocols for early diagnosis (e.g., observation or extravasation detection accessories for high-risk patients) [66]. Furthermore, protocols can be implemented to reduce contrast extravasation-related complications from PIVCs and should be updated regularly [87]. For instance, use of a four-phasic contrast media administration protocol was associated with a 65% reduction in extravasations versus a three-phasic approach in cardiac CT angiography [87]. This protocol, distinguished by the saline pacer bolus, is easy to implement and has no additional costs. Similarly, a quality-improvement study involving contrast-enhanced CT, found a statistically significant reduction in IV contrast extravasation after modifying the intake process (0.47% of patients [38/8,009] preintervention versus 0.28% [24/8,521] postintervention, P = 0.04) [82].

Importantly, staff should receive continuous education on all aspects related to risk of infiltration and extravasation and always document and report any case that occurs.

Discussion and Future Directions

This narrative review characterizes the incidence, symptoms, modifiable and non-modifiable risk factors, and clinical and economic consequences of PIVC-related infiltration and extravasation, as well as strategies for prevention. This evidence applies to a broad range of patients and includes some large, multicentre studies, systematic reviews, and meta-analyses. This review showed that infiltration occurs in up to 20% of PIVCs, making it the second most common PIVC complication. Although generally reported to be less frequent than infiltration, extravasation is sometimes associated with more severe consequences, and the incidence varies between different types of extravasations (e.g., contrast / radiopharmaceutical, chemotherapy, and vasopressor). However, it is likely that these rates are underestimated, as many cases may go undocumented [17].

The type of medication or solution infused determines whether infiltration or extravasation will occur, and both modifiable and no modifiable risk factors are associated with PIVC-related infiltration and extravasation. While initial signs and symptoms of these events appear immediately, some physical symptoms can arise days to weeks later [20]. Thus, education for and monitoring by patients and clinicians is critical to enable timely detection, diagnosis, and treatment. Key published guidance includes the Infusion Therapy Standards of Practice, which aims to promote consistency in patient care, inform clinical decision-making, and improve skill [4]. When infiltration or extravasation occurs, conservative acute treatments are often recommended (e.g., limb elevation), with limited evidence for more invasive treatments.

Infiltration and extravasation are associated with important clinical and economic burdens. While the severe sequalae of infiltration and extravasation may not be frequent, when these harms occur, they can have serious consequences, such as functional deficits, chronic pain, and possible limb loss. Management of these consequences is costly, including additional hospital stay, emphasizing the need for more consistent implementation of preventative strategies to reduce the risk of these events given the substantial volume of PIVC insertions in healthcare settings. Preventative measures include techniques and protocols around the equipment, insertion site, administration, and monitoring, with patient and clinician education being crucial to successful procedures and responsive monitoring of complications.

Although the most recently available data related to infiltration and extravasation was included, some evidence gaps were identified. First, there is a lack of literature on the economic

burdens of infiltration and extravasation; most studies looked at overall costs related to complications, rather than providing a comprehensive assessment of the different cost types involved. Second, since multiple insertions are a risk factor for extravasation [11,12,19], further research evaluating strategies and protocols for improving first time PIVC insertion success are warranted. Third, additional studies assessing the importance of hospital setting as a risk factor are needed; in one prospective cohort from Australia, infiltration accounted for 32% of all post-insertion failures of ED-inserted PIVCs [90]. This finding emphasizes the need for educational training for all staff inserting PIVCs, especially in certain settings. Finally, although use of a reliable, validated, and standardized assessment tool for infiltration/extravasation is recommended, few assessment scales have been published, and only one pediatric tool has been tested for validity and interrater reliability [4]. Development, validation, and reliability testing of assessment tools are needed to address this important component of infiltration/extravasation diagnosis and assessment.

This narrative review has limitations. First, it was informed by a TLR rather than a specific systematic review. This was intentional so the broad scope of this review was feasible, and a defined search methodology was still used. As such, it is possible that some relevant papers were missed. Second, most of the data involved smaller observational studies. However, wherever possible, clinical guidelines, RCTs, systematic reviews, and meta-analyses were included and discussed. Finally, this review outlines the evidence on PIVC infiltration and extravasation, diagnosis, treatment, and prevention strategies, but all clinicians are recommended to review manufacturer's indications for use before considering product options in their region or setting of care.

As demonstrated in this review, infiltration and extravasation are common complications of PIVC use. Future research should focus on preventative efforts, including RCTs, to reduce the clinical and resulting economic burdens associated with infiltration and extravasation. Despite the evidence presented in this narrative review of the burdens associated with PIVC-related infiltration and extravasation, clinicians routinely insert PIVCs in most patients reflexively. In actual practice, when considering PIVC insertion, more time needs to be devoted to the awareness of: (1) decision-making in the context of the clinician's own experience, (2) cognitive biases and (3) patient-centered factors. Such awareness will support an appropriate risk assessment, which will benefit the patient, clinician, and healthcare system.

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