emergency care and medicine

MDPI

Systematic Review

Peripheral Norepinephrine Administration in Critically Ill Adults: A Rapid Review of Administration Practices and Reported Local Adverse Events

Beatriz Ramos Serápio *, Helena José * and Isabel Rabiais *

Atlântica School of Health Sciences, Universidade Atlântica, 2730-036 Barcarena, Portugal
* Correspondence: 2023119@uatla.pt (B.R.S.); hjose@uatla.pt (H.J.); irabiais@uatla.pt (I.R.)

Abstract

Background: Peripheral norepinephrine enables timely vasopressor initiation, but local safety remains uncertain. This rapid review mapped administration practices and local adverse events in critically ill adults. Methods: Following Joanna Briggs Institute and Cochrane rapid review guidance and PRISMA 2020 (OSF: 10.17605/OSF.IO/6VH9E), PubMed, MEDLINE Complete and CINAHL Complete were searched through 22 August 2026 (PubMed re-run with corrected syntax within this limit). Included syntheses were citation-searched. Short peripheral intravenous and midline catheters were analysed separately; peripherally inserted central catheters were classified as central access. Results: Thirty-nine sources were included (27 primary studies, seven syntheses, five normative documents); three reports were unavailable. In 14 norepinephrine-specific reports using short peripheral catheters, source-defined extravasation or infiltration occurred in 0–5.6% of patients or infusions, and with midline catheters in one of 472 episodes; composite local events were analysed separately. Serious injury was inconsistently assessed; one fasciotomy occurred among 3734 patients in a mixed-agent cohort. Confidence was low to very low for all outcomes. Conclusions: Observational evidence suggests that peripheral norepinephrine is feasible in selected critically ill adults under structured monitoring and extravasation-response protocols, with infrequent, mostly minor events, but does not establish comparative safety or universal concentration, dose or duration limits.

Keywords: norepinephrine; catheterisation; peripheral; vasoconstrictor agents; extravasation of diagnostic and therapeutic materials; patient safety; critical care; critical illness

Check for updates

Academic Editor:
Raimundas Lunevicius

Received: 22 September 2026
Revised: 2 November 2026
Accepted: 3 November 2026
Published: 5 November 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

Norepinephrine is the first-line vasopressor recommended for the treatment of septic shock [1]. Because errors in its preparation or administration may have severe consequences, it is also included in the list of high-alert medications of the Institute for Safe Medication Practices [2].

Norepinephrine has traditionally been administered through a central venous catheter (CVC), largely because of concern about extravasation, ischaemia and tissue injury. However, central access is invasive, may cause mechanical, thrombotic and infectious complications, and may delay the start of vasopressor support [1,3,4].

The 2026 Surviving Sepsis Campaign (SSC) guidelines suggest starting vasopressors peripherally when waiting for central venous access would delay restoration of mean arterial pressure. This recommendation applies to adults with septic shock, is conditional, and is based on evidence of very low certainty [1].

Peripheral use of vasopressors, predominantly norepinephrine in the available cohorts, has been studied in intensive and intermediate care, emergency departments and resource-limited settings. In general, studies have reported low frequencies of extravasation in cohorts managed under protocols that include access selection, confirmation of patency and regular monitoring [5–12], although not all of them report outcomes attributable specifically to norepinephrine, and these observational designs do not establish that individual protocol components prevent injury.

Several systematic reviews have summarised the literature and reported low pooled frequencies of extravasation and of other serious complications [4,13–16]. However, they combine different vasoactive agents, short peripheral catheters, midline catheters and, in some cases, centrally positioned catheters, as well as studies published over several decades; the underlying evidence is largely observational, and studies differ in population, concentration, dose, infusion duration and the definition of adverse events [3,4,13,17]. Beyond extravasation, complications such as infiltration, phlebitis, thrombosis, infection, ischaemia and tissue injury have been described [13,18].

Guidance documents and institutional protocols aim to reduce these risks through appropriate vessel selection, use of a dedicated line, frequent assessment of the insertion site and pre-defined management of extravasation [17,19–22].

Despite these common elements, differences persist regarding catheter site and gauge, concentration, dose, duration of administration, monitoring frequency and the timing of transition to central access. For this reason, thresholds defined by an individual service should be understood as local decisions rather than universal recommendations [3,4,13,20].

It is therefore important to bring together the available evidence and to analyse the findings of primary studies, reviews and normative documents separately. This separation makes it possible to identify the most frequently recommended practices, to recognise areas of persisting uncertainty, and to avoid presenting local protocols as universal recommendations. It is equally necessary to distinguish evidence that is directly attributable to norepinephrine from evidence derived from cohorts exposed to several vasoactive agents, a distinction that is rarely made explicit in the existing literature.

Recent syntheses are particularly relevant. Fernández-Ginés et al. [3] addressed peripheral norepinephrine specifically, but synthesised the evidence narratively and had limitations in its search and appraisal methods; Chen et al. [17] summarised the best available evidence on the management of vasopressors through peripheral catheters, producing operational recommendations without event frequencies; Wu et al. [13] pooled extravasation, thrombosis and infection across vasopressors and across short peripheral catheters, midlines and peripherally inserted central catheters (PICCs); and ZhangJian et al. [16] pooled 49 studies of peripheral vasopressors, with subgroup estimates by agent and catheter type. The present review does not seek to produce a further pooled estimate. Instead, it adds four elements: (i) an outcome-level separation of norepinephrine-specific from mixed-agent evidence, reporting for each outcome the exposed denominator, the unit of analysis and the 95% confidence interval (CI); (ii) separate analysis of short peripheral and midline catheters, with PICCs treated as central access; (iii) a structured assessment of confidence in key safety findings and a mapping of overlap between reviews; and (iv) a mapping of the practices recommended in normative documents, appraised separately so that local thresholds are not presented as universal limits.

Accordingly, this rapid review addresses the following question: in critically ill adults receiving norepinephrine through peripheral venous access, what practices, conditions of administration and monitoring measures are used, and what local adverse events are reported? The objective is to identify and synthesise those practices, conditions and monitoring measures and to describe the local adverse events reported, distinguishing evidence

attributable to norepinephrine from evidence derived from mixed-agent cohorts, and evidence from short peripheral catheters from that from midline catheters.

2. Materials and Methods

2.1. Design and Methodological Guidance

This study is a rapid review, a form of evidence synthesis in which components of the systematic review process are simplified or omitted to produce evidence in a shorter time [23]. It followed the JBI principles of rigour, transparency and applicability [24,25], with adaptations supported by Cochrane rapid review guidance [23], without claiming full conformity with a Cochrane review. Reporting followed PRISMA 2020 [26]. A rapid approach was chosen because the review was intended to inform clinical practice within a limited time frame and with limited resources.

The steps abbreviated relative to a full systematic review were the restriction of searching to three databases, without Embase, the Cochrane Library or trial registries; date (from 2016) and language restrictions; use of a full-text limiter in the two EBSCOhost databases; searches for normative documents that were only partly documented; and a structured, GRADE-informed judgement of confidence instead of a full GRADE assessment. Screening, full-text assessment, data extraction and critical appraisal were not abbreviated and were performed independently by two reviewers. These adaptations were defined in the protocol, except where identified as amendments (Section 2.2 and Table S10).

The review was designed as a rapid systematic review of primary evidence, complemented by a structured mapping of evidence syntheses and normative documents. Because these source categories answer different questions, each was given a distinct role (Figure 1). Primary studies formed the core synthesis of local adverse events and of the practices observed. Evidence syntheses were used as contextual evidence—for comparison with previous pooled estimates and for citation searching—but their estimates were not combined with primary data or used as independent corroboration. Normative documents were used only to map recommended practices, which are reported as context-dependent practices rather than as evidence of effectiveness.

2.2. Protocol Registration

The protocol was registered with the Open Science Framework as version 1.1 of 26 August 2026 and updated to version 1.2 of 16 September 2026, which consolidates the amendment log (https://doi.org/10.17605/OSF.IO/6VH9E). Registration took place after the search and selection of documents had been completed, but before formal data extraction, critical appraisal and synthesis; it was therefore retrospective with respect to searching and selection, and prospective with respect to the subsequent stages. Version 1.1 described selection as having been conducted by a single reviewer. Selection had in fact been carried out independently by two reviewers, with disagreements resolved by discussion, so version 1.2 corrects the registered description of a stage that was already complete rather than recording a later change in procedure. Data extraction and critical appraisal, undertaken after registration, were likewise performed independently by two reviewers, which strengthens the method initially described. Both points are recorded in the amendment log (Table S10). Several eligibility and analysis decisions were made or specified after study selection, and some during peer review (Section 2.4). Because they were taken with knowledge of the candidate studies, these decisions and the retrospective registration are potential sources of bias; their influence was examined, where possible, in a sensitivity assessment (Section 3.7.5) and is discussed in Section 4.4. The protocol was updated to version 1.3 to record Amendments 6–11, and to version 1.4 to record Amendment 12, made during the second round of peer review (Table S10).

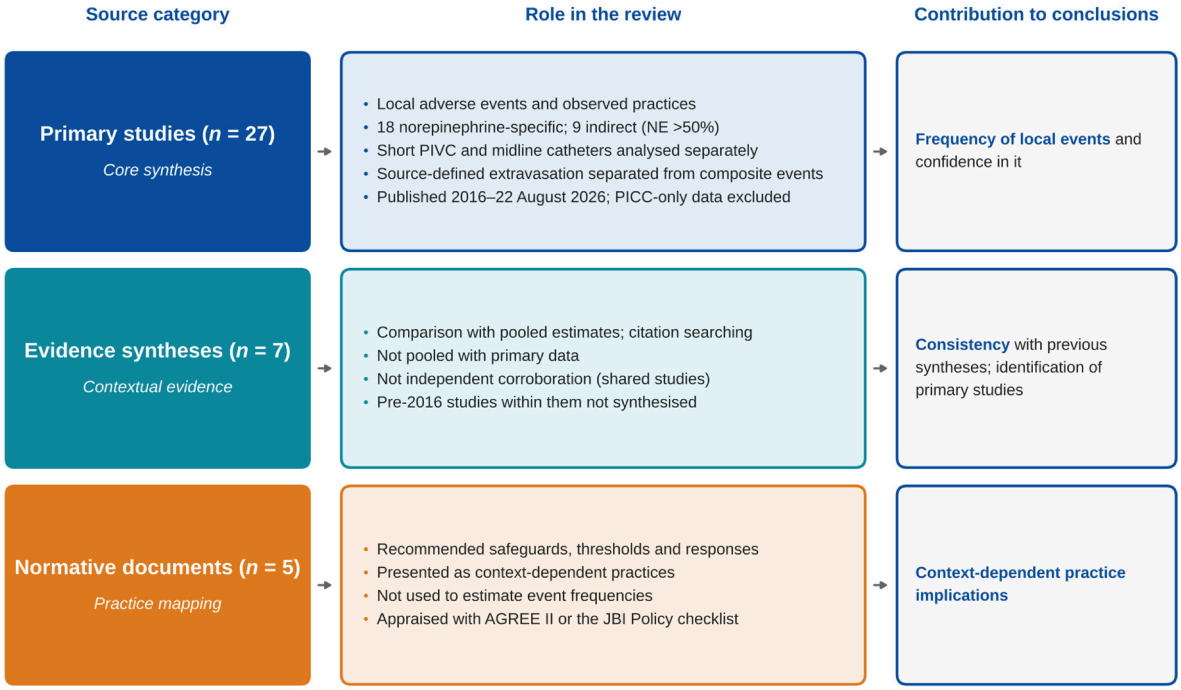


Figure 1. Structure of the review: role of each source category and its contribution to the conclusions. NE, norepinephrine; PICC, peripherally inserted central catheter; PIVC, peripheral intravenous catheter.

2.3. Review Question and PCC Framework

The review question and eligibility criteria were structured according to the PCC model—population, concept and context—as appropriate for a broad question addressing practices, safety conditions and different types of sources [24]; its elements are presented in Table 1.

Table 1. PCC structure of the review question.

Element	Definition
Population	Adults (≥18 years) who are critically ill.
Concept	Practices, safety conditions and local adverse events in the administration of norepinephrine through peripheral venous access (short peripheral intravenous catheter or midline catheter).
Context	Intensive and intermediate care, emergency and urgent care, resuscitation and prehospital emergency care.

2.4. Eligibility Criteria

For the purposes of this review, peripheral venous access was defined as a device inserted into, and terminating in, a peripheral vein: the short peripheral intravenous catheter (PIVC) and the midline catheter. These two devices differ in length, insertion technique, dwell time and tip position—the tip of a midline catheter lies in an upper-arm vein at or below the level of the axilla—and have different risk profiles; they were therefore analysed separately throughout the synthesis, and results combining both devices were reported as such. The PICC was not considered peripheral access: when its tip is centrally positioned, the infusion is central, irrespective of the peripheral insertion site. Results obtained exclusively through PICCs were excluded, and estimates that pooled PICCs with peripheral devices were retained only as clearly identified contextual evidence. This definition was corrected during peer review (Table S10, Amendment 6), replacing an earlier definition that had included PICCs; the correction did not change the set of included sources.

Three distinct categories of normative document were considered and treated separately throughout the article: international guidelines issued by scientific societies, clinical guidance issued by professional societies, and institutional protocols of local scope.

With respect to the drug, the criterion was operationalised at two levels after data extraction (Table S10, Amendment 4), and its quantitative threshold was specified during the peer review (Amendment 7). Studies in which only norepinephrine was administered peripherally, or in which events were reported by agent or by treatment group or explicitly attributed to patients receiving norepinephrine, were included as norepinephrine-specific evidence. In the absence of such separation, studies in which norepinephrine was the predominant agent—defined as more than 50% of exposed patients receiving norepinephrine, as reported by the source—were included and classified as indirect evidence. This threshold corresponds to a simple majority; it was chosen on that conceptual basis rather than derived from the event rates of the candidate studies, but because it was specified after those rates were known, its influence was examined in a sensitivity assessment (Section 3.7.5). Studies were excluded when norepinephrine accounted for 50% or less of the exposure, or when the agent infused through the peripheral catheter could not be established, and events were not reported by the agent. The criterion was applied to every mixed-agent cohort assessed in full text, including those identified during the revision (Section 3.3). The eligibility criteria are summarised in Table 2. Decisions made or modified after study selection, and their potential influence, are summarised in Table 3.

Table 2. Inclusion and exclusion criteria.

Domain	Inclusion	Exclusion
Population	Critically ill adults; adult data separable in mixed samples.	Exclusively paediatric or neonatal populations; non-separable adult data; samples admitting participants under 18 years without separable results.
Drug	Norepinephrine; multi-vasopressor studies in which events are separable by agent (norepinephrine-specific evidence), or in which norepinephrine is the predominant agent (>50% of exposed patients; indirect evidence).	Other vasopressors with no identification of norepinephrine exposure; studies in which norepinephrine accounts for ≤50% of the exposed cohort, or in which the agent infused peripherally cannot be established, and events are not reported by agent (criterion specified post hoc; Table S10).
Route	Peripheral venous access: short PIVC or midline catheter (tip in a peripheral vein), analysed separately; protocols for peripheral initiation and transition.	Central venous administration, including PICCs and other centrally positioned catheters; PICC-only results; intraosseous or arterial administration. Estimates pooling PICCs with peripheral devices: contextual evidence only.
Outcomes	Safety, infiltration, extravasation, tissue injury, catheter failure, monitoring and incident response.	Haemodynamic efficacy without data on the safety of the peripheral route.
Context	Critical, intensive or intermediate care, emergency and urgent care, shock or critically ill patients.	Outpatient, home or non-critical settings without applicability.
Source type	Primary studies; systematic reviews and evidence syntheses; normative documents in the three categories defined above.	Study protocols without results; editorials, abstracts or materials without substantiated recommendations.
Period and language	January 2016 to 22 August 2026 (publication date limit, retained in the corrected PubMed re-run of 16 October 2026); Portuguese, English or Spanish. Primary studies identified through citation searching had to meet the same criteria.	Outside the period or in other languages.

Table 3. Decisions made or modified after study selection and their potential influence.

Decision	Protocol (Planned)	Modification and Timing	Potential Influence and How It Was Examined
Protocol registration	Registration before the review stages	Registered on 26 August 2026, after searching and selection and before extraction, appraisal and synthesis	Selection decisions not protected by registration; all subsequent changes recorded in the amendment log (Table S10)
Number of reviewers at selection	Version 1.1 described a single reviewer	Corrected in version 1.2: selection had been performed by two independent reviewers (Amendment 5)	Correction of the registered description; no change in procedure
Mixed-agent cohorts	Norepinephrine; no rule for cohorts exposed to several agents	Two-level criterion after data extraction (Amendment 4); threshold of >50% specified during peer review (Amendment 7)	Determined the inclusion of nine indirect studies and the exclusion of four [27–30]; criterion applied to all mixed cohorts (Section 3.3); sensitivity assessment (Section 3.7.5)
Definition of peripheral access	Short PIVC, midline or PICC	PICC reclassified as central access; short PIVC and midline analysed separately (peer review; Amendment 6)	No source added or removed; pooled PICC-inclusive estimates [13] treated as contextual only
Outcome data items	Complications, monitoring and response	Unit of analysis, definitions, surveillance, follow-up and exposure time added (peer review; Amendment 8)	Re-extraction from full texts by two reviewers (Table S17)
Search and retrieval	Searches of 22 August 2026; reference screening	PubMed search re-run on 16 October 2026 with corrected syntax and the original date limit; systematic citation searching of all included syntheses; further retrieval attempts, including contact with authors and a co-author's institutional access (peer review; Amendments 9 and 10)	21 primary studies and three syntheses added; three reports not retrieved (Section 4.4)
Confidence in findings	Not specified	Structured GRADE-informed assessment added (peer review; Amendment 11)	Ratings and their justification reported in Section 3.8; revised under Amendment 12
Outcome classification and imprecision	Local events as reported; imprecision not specified	Composite or nonspecific local events separated from source-defined extravasation or infiltration; imprecision judged from study-level CIs against 5% and 10% limits (second peer review; Amendment 12)	Two overlapping reports [31,32] moved to a separate category without changing the range of extravasation or infiltration; confidence for one outcome depends on the limit chosen (Section 3.8)

PICC, peripherally inserted central catheter; PIVC, peripheral intravenous catheter. Dates, reasons and the version of the protocol affected by each amendment are given in Table S10.

2.5. Information Sources and Search Strategy

Final searches were conducted on 22 August 2026 in PubMed, MEDLINE Complete and CINAHL Complete. PubMed was searched through its native interface; MEDLINE Complete and CINAHL Complete were searched through EBSCOhost. Indexed and free-text terms relating to norepinephrine or vasopressors and to peripheral administration were combined. The main combination comprised the norepinephrine/vasopressor and peripheral administration blocks. A focused combination additionally applying the population and context blocks was also run; because it is a subset of the main combination within each database, it served only as a check on retrieval and contributed no additional unique records. Safety and context blocks were documented but not required in the main combination to reduce the risk of missing relevant studies. No paediatric exclusion block was applied; this exclusion was performed during screening. In each database, filters for publication date (1 January 2016 to 22 August 2026) and language (Portuguese, English or Spanish) were applied; in MEDLINE Complete and CINAHL Complete, the EBSCOhost full-text limiter

was also applied. This limiter restricts retrieval to records with full text available through EBSCOhost and may have excluded eligible records, particularly nursing studies indexed in CINAHL Complete; the PubMed search, to which it was not applied, and citation searching reduce this risk but cannot establish that no eligible study was excluded (Section 4.4). The exact executed strings, field codes and filters are presented in Tables S1–S3.

During peer review, two eligible studies that were missing from the review were brought to our attention: one had not been retrieved by the original strategy [10], and the other had been retrieved in August but excluded in error at title and abstract screening [16]. The PubMed search was therefore re-executed on 16 October 2026 with the same limits, using the strategy in Tables S1 and S5 after correction of formatting errors found in the strategy as reported (typographic quotation marks, phrases without quotation marks and inconsistent hyphenation). The main combination retrieved 458 records without filters (456 in August 2026) and 152 with filters (150 in August 2026); the two additional records were screened in the same way. Restricting the re-run search to records added to PubMed after 22 August 2026 returned no records, indicating that the additional records were retrieved because of the corrected syntax rather than new indexing; one of them was Medlej et al. [10]. Because the re-run retained the publication date limit of 22 August 2026, it corrected the August search rather than extending it; the eligibility window of the review ends on 22 August 2026 for all searches, including citation searching, and no primary study or evidence synthesis published after that date was included. MEDLINE Complete and CINAHL Complete were not re-searched, which is acknowledged as a limitation (Section 4.4).

The 2016 start date was chosen to capture contemporary practice—current infusion technology, vascular access devices and the protocol-based approach recommended in recent guidance—within the time constraints of a rapid review. Primary studies published before 2016 were not eligible, including those identified through the included systematic reviews (Section 2.10).

PubMed and MEDLINE Complete overlap substantially. PubMed was searched to capture records not yet indexed, or not indexed, for MEDLINE (in-process, ahead-of-print and PubMed Central-only records), whereas MEDLINE Complete was searched through EBSCOhost to apply subject-heading strategies consistent with CINAHL Complete, which was included for its coverage of the nursing literature on infusion and vascular access practice. The resulting overlap was handled by de-duplication (Section 2.7). Embase, the Cochrane Library and multidisciplinary citation databases were not searched; this restriction is acknowledged as a limitation (Section 4.4) and was partly mitigated by citation searching of the included syntheses.

2.6. Supplementary Searching and Grey Literature

Complementary searches for normative documents were conducted on the websites of the Intensive Care Society, the Portuguese Directorate-General of Health and the NSW Agency for Clinical Innovation on 22 August 2026, using the terms “peripheral noradrenaline”, “peripheral norepinephrine”, “peripheral vasopressor” and “extravasation”, together with their Portuguese equivalents, and on the website of the Society of Critical Care Medicine/Surviving Sepsis Campaign on 26 August 2026. Between 22 and 26 August 2026, targeted searches of professional-society and institutional websites and of reference lists were also performed, through which the three institutional protocols were identified. The documents were retrieved from the websites of the issuing organisations [19–22] or from their journal publication [1]. The number of results screened on each website was not recorded and the targeted searches were not documented in detail, so this step is only partly reproducible, which is acknowledged as a limitation (Section 4.4). Five normative documents were included: the international Surviving Sepsis Campaign 2026 guideline,

the guidance of the Intensive Care Society, and three institutional protocols of the National Health Service (NHS), issued by the Royal Cornwall Hospitals NHS Trust, the Gloucestershire Hospitals NHS Foundation Trust and the Worcestershire Acute Hospitals NHS Trust [1,19–22].

Normative documents were considered eligible when they presented institutional authorship, an identifiable date or version, relevant operational recommendations and a scientific rationale. They were extracted and presented separately from primary studies and reviews and were not used in the calculation of adverse event frequencies.

The reference lists of the included sources were screened for additional primary studies. In response to the peer review, this citation searching was repeated systematically for all seven included evidence syntheses, including the 49 studies included by ZhangJian et al. [16]. Candidate studies were screened against the eligibility criteria of Table 2; studies already assessed through the database searches were not counted again, and studies published before 2016, conducted in other populations or settings, or addressing other agents only were excluded at this stage. The candidates screened, with the reason for each exclusion, are listed in Table S8.

2.7. Reference Management and Selection

All six filtered result sets of August 2026—the main and the focused combinations in each of the three databases (381 records; Table S4)—were exported to Rayyan (web application; https://www.rayyan.ai, accessed on 18 October 2026), where de-duplication was performed and eligibility decisions were recorded [33]. Because the focused combination is a subset of the main combination within each database, its 114 (63 in PubMed, 12 in MEDLINE Complete and 39 in CINAHL Complete) duplicated records were already retrieved by the main combinations and were removed as within-database duplicates; the remaining 36 duplicates were records retrieved by more than one database, mainly PubMed and MEDLINE Complete. Potential duplicates were flagged by the Rayyan duplicate-detection function and confirmed manually before removal, leaving 231 unique records, to which the two additional records of the corrected PubMed re-run were added. Title and abstract screening and full-text assessment were performed independently by two reviewers, with disagreements resolved by discussion. Reasons for full-text exclusion were recorded, and reports that could not be obtained were classified separately as reports not retrieved. Full texts were sought through institutional subscriptions, the university library, b-on, Google Scholar, the RCAAP repository, the Cochrane Library, open-access repositories and publishers' websites; during the peer review, unretrieved reports were sought again, corresponding authors were contacted by e-mail and, where no address was available, requests were made through ResearchGate; during final verification, all reports still unretrieved were checked for open-access copies in OpenAlex (web database; https://openalex.org, accessed on 18 October 2026), an open bibliographic index, and two further reports were obtained through the institutional access of a co-author. Each attempt and its outcome is recorded in Table S6.

2.8. Data Extraction

Data extraction was performed independently by two reviewers, with disagreements resolved by discussion, using a form that was piloted on the first sources and adjusted before being applied to the remaining documents. Information was extracted on identification, design, population, context, vascular access, concentration, dose, duration, monitoring, complications, incident response and transition criteria. Sources added during the revision were extracted with the same form. The completed extraction dataset is provided as Supplementary File S2.

The form included a dedicated norepinephrine specificity field, recording the proportion of the sample exposed to the drug, whether separable results were available (yes or no), the applicable specific denominator, and attribution of the event to norepinephrine (yes, no or uncertain). Data were confirmed in the full text and recorded with an indication of the corresponding page, table or section. Where information was unavailable, it was recorded as "not reported". For each local adverse event, the device (short PIVC or midline catheter), the unit of analysis (patient, infusion, episode or catheter), operational definition and grading system, surveillance frequency, observation period after the end of infusion, missing or incomplete assessments, exposure time and any exposure-adjusted estimate were also extracted (Tables S17 and S18); these items were added during the peer review (Table S10, Amendment 8). The complete form is presented in Table S9.

2.9. Critical Appraisal

Primary studies were appraised with the JBI Critical Appraisal Checklist for Cohort Studies and evidence syntheses with the JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses (both in their 2020 versions) [34]; the wording of each question is given in Tables S12–S14. The Surviving Sepsis Campaign 2026 guideline was appraised with AGREE II [35]. The Intensive Care Society guidance and the three institutional protocols were appraised with the JBI Critical Appraisal Checklist for Textual Evidence: Policy/Consensus Guidelines [36]. The single randomised trial, which allocated the timing of CVC insertion in participants who all started norepinephrine peripherally, was appraised with the cohort checklist because only the frequency of local events among exposed participants was extracted [37].

Critical appraisal was performed independently by two reviewers, with item-by-item justification and disagreements resolved by discussion. Consistent with JBI guidance, results are presented item by item, without conversion into aggregate scores or application of cut-off values, since these are not validated. No source was excluded on the basis of critical appraisal; judgements were used to weigh confidence, applicability and currency. Detailed results are presented in Tables S12–S14. For AGREE II, the two appraisers rated each item independently and agreed on the rating of every item, from which scaled domain scores were calculated (Table S15).

Confidence in key safety findings was assessed at the outcome level by two reviewers, using a structured judgement informed by the GRADE domains—risk of bias, inconsistency, indirectness, imprecision and missing evidence (publication or reporting bias)—adapted to a synthesis without pooled estimates (Section 3.8). Imprecision was judged from the study-level 95% CIs rather than from combined denominators, and a central comparator was required only for the comparative question (Section 3.8).

2.10. Synthesis

A narrative synthesis supported by tables and figures was performed, structured by source category (Figure 1). Primary studies formed the core synthesis. Evidence syntheses were presented separately from the primary studies, and their pooled estimates were neither combined with primary data nor used as independent corroboration, because they share primary studies with one another and with the present review (Table S19) and include studies published before 2016, other agents and, in one case, PICCs. Normative documents were analysed separately and used only to map recommended practices. Meta-analysis was not performed because of differences in populations, agents, devices, surveillance and definitions of adverse events, and because pooling rare-event proportions from uncontrolled cohorts with different exposure times would produce an estimate of spurious precision.

Results were organised according to the characteristics of vascular access, concentration, dose, duration, patency, monitoring, local complications, risk factors, incident response, antidotes, local measures and criteria for placement of central venous access.

In studies including multiple vasopressors, quantitative results were attributed specifically to norepinephrine only where the source allowed both the administered agent and the corresponding event to be identified. In all other cases, results were presented as indirect evidence on peripheral administration of vasopressors, with explicit indication of the denominator used by the original source.

Outcomes were synthesised separately by device and by outcome: patient-, infusion- or episode-level extravasation or infiltration was kept separate from catheter-level phlebitis and from thrombotic and infectious complications. Events were counted as extravasation or infiltration only when the source defined or labelled them as such; composite or nonspecific local events whose components could not be separated (for example, a single category of irritation, infiltration or phlebitis) were reported in a separate category and were not counted as extravasation (Table S10, Amendment 12). For each proportion, the exposed denominator and an exact (Clopper–Pearson) 95% CI recalculated by the reviewers from the reported counts are presented for every study; where a source reported a proportion or CI obtained with another method, the source value is given separately and labelled as reported. Where a source distinguished confirmed from possible events, both are reported. Exposure-adjusted rates are reported as supplied by the sources, and proportions were not compared directly across studies with markedly different infusion durations.

Older evidence and overlapping populations were handled as follows. A primary study identified through an included synthesis entered the core synthesis only if it met all eligibility criteria, including publication in or after 2016; older studies therefore contributed only through the pooled estimates of the syntheses, which were reported as contextual evidence. Where several reports described the same cohort, the most complete report was used and the cohort was counted once; the pilot and post-implementation reports of one programme [31,32], which cover different but overlapping periods with their own denominators, were analysed as two studies, and their overlap is stated wherever they are used (Section 3.1). Overlap of primary studies across the included syntheses was mapped (Table S19). A sensitivity assessment examined whether the conclusions changed under alternative decisions on attribution, the predominance threshold, the inclusion of possible events and device type.

3. Results

3.1. Selection of Sources

The database searches of August 2026 identified 381 records, including 114 records from the focused combinations that duplicated records retrieved by the main combinations (Section 2.7), and the corrected PubMed re-run identified two additional records. After removal of 150 duplicates, 233 records were screened by title and abstract and 204 were excluded. Twenty-nine reports were sought for retrieval; three were not retrieved and 26 were assessed for eligibility. Six were excluded: three narrative reviews, one conference abstract, one study that admitted participants aged 16–17 years without separable data [38] and one mixed-agent cohort in which norepinephrine accounted for 41% of the exposure without events reported by the agent [27], under the drug criterion specified after data extraction (Table S10). Twenty reports from the databases were included. Through other methods, five normative documents were identified on the websites of issuing organisations, and citation searching of the included syntheses identified 36 records not previously assessed, of which 19 were sought and retrieved in full text; 14 were included and five were excluded: one because it included participants younger than 18 years without separable data, two

because exposure to norepinephrine was not quantified and the results of patients receiving vasopressors were not reported by the agent [29,30], one because norepinephrine was a minority agent among patients who received peripheral vasopressors only and the agent infused peripherally was not reported for the remaining patients [28], and one because it estimated the potential avoidance of central venous catheters from the dose and duration data without evaluating peripheral administration or reporting local events [39]. Two of the included reports described the same peripheral vasopressor programme, a three-month pilot [31] and a 12-month post-implementation cohort [32]; because they are separate publications with their own denominators, they were analysed as two studies, but their periods overlap, so some patients are probably included in both and the two estimates are not independent. In total, 39 sources were included (27 primary studies, seven syntheses and five normative documents), and three reports were not retrieved (Figure 2). The reports not retrieved, with the retrieval attempts made for each, and the full-text exclusions, with reasons, are listed in Tables S6 and S7.

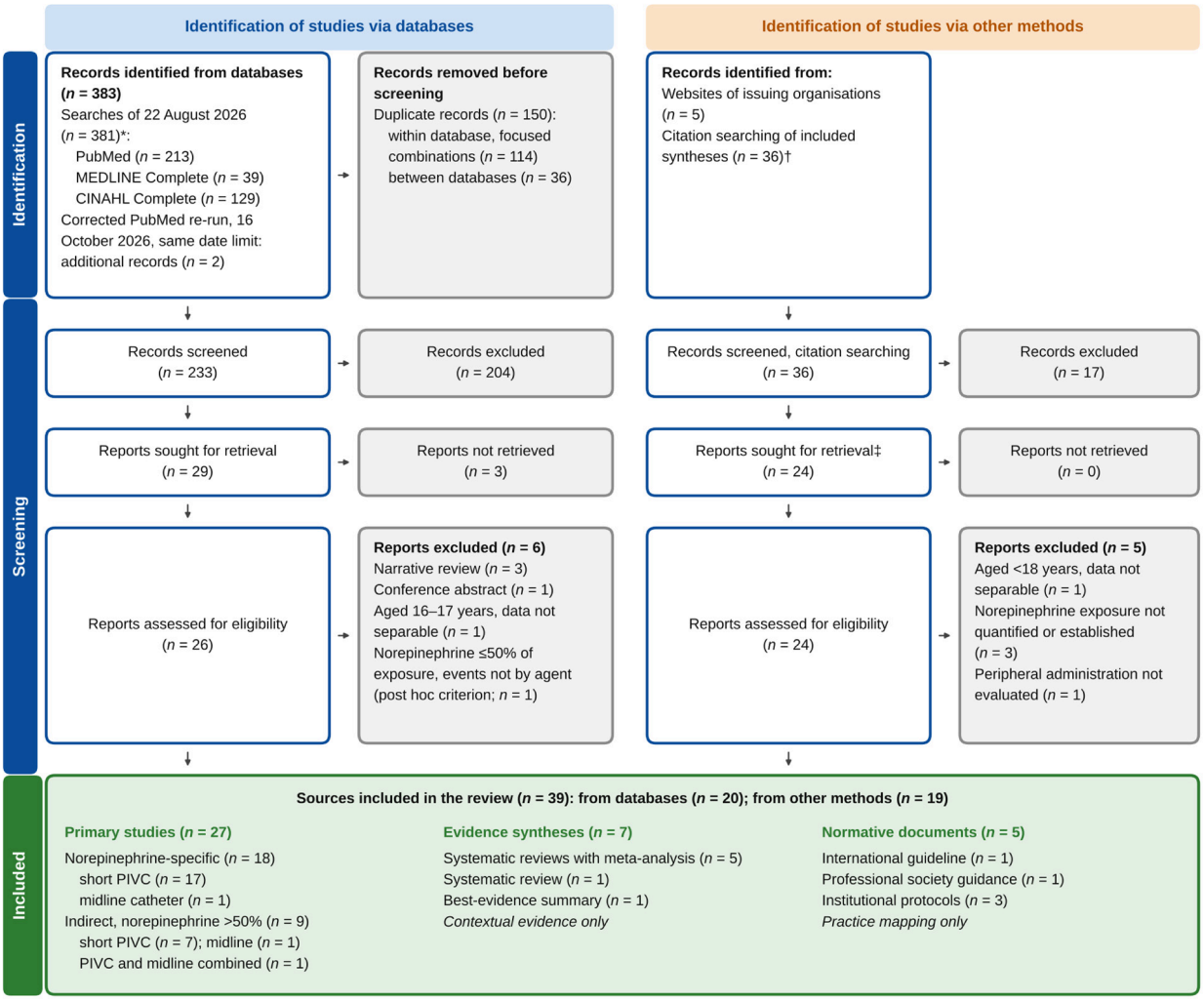


Figure 2. PRISMA 2020 flow diagram of the identification and selection process. * All filtered results of the main and focused search combinations were exported; focused-combination records duplicated those of the main combinations (Section 2.7). † Records from the reference lists of the included syntheses not previously assessed; candidates and reasons for exclusion are listed in Table S8. ‡ Including the five normative documents identified on the websites of issuing organisations. PIVC, peripheral intravenous catheter.

3.2. Characteristics of the Included Sources

The 34 scientific publications comprised 27 primary studies, with data collected directly from participants, and seven evidence syntheses. The primary studies were published between 2017 and 2026 and were conducted in intensive, intermediate and cardiac care units, emergency departments and, in one low-resource hospital without an intensive care unit, the emergency department and medical ward [40]. They came from the United States ($n = 14$), Australia and Sweden ($n = 2$ each), India, Singapore, Japan, Ethiopia, Lebanon, Italy, Israel and Uganda ($n = 1$ each), and one was multinational [41] (Table 4). Nine were prospective cohorts, 14 were retrospective cohorts, three were secondary analyses of prospective studies or trials [6,18,41] and one was a randomised feasibility trial [37]; eight were multicentre [6,8,18,41–45]. None randomised patients to peripheral or central administration: the trial randomised the timing of CVC insertion (within 4 h or after 12 h) in patients who all started norepinephrine peripherally [37]. Six studies compared patients according to the route of initiation [6,41,44–47], one compared peripheral norepinephrine with peripheral metaraminol [48], and two compared periods before and after implementation of a peripheral vasopressor protocol, one recording local events only after implementation [32] and one in both periods [49]. The five normative sources comprised one international guideline, one professional society guidance document and three NHS institutional protocols.

Eighteen primary studies reported local events attributable to norepinephrine: in eight, only norepinephrine was administered peripherally [9,12,40,43,50–53]; in seven, events were reported by agent or by treatment group [11,18,31,32,42,48,49]; and in three, the source stated that all events occurred in patients receiving norepinephrine [5,7,10]. In Goh et al. [5], this allowed a norepinephrine-specific denominator (180 exposed patients) to be applied; because co-administration of other vasoactive agents in the two patients with events is not reported, this attribution should be interpreted with caution. In the remaining nine, norepinephrine was the predominant agent (from 57.6% of exposed patients to the initial agent in all participants), but events were reported for vasoactive agents as a whole; these constitute indirect evidence [6,8,37,41,44–47,54]. The application of the predominance criterion to every mixed-agent cohort is shown in Table 5. Twenty-four studies used short PIVCs only, two used midline catheters only [43,54] and one included both without separating results by the device [6]; none reported administration through PICCs.

Table 4. Characteristics of the included primary studies, by attribution and device.

Study	Design; Country; Setting	*n* (NE-Exposed)	Device; Gauge; Site	NE Concentration, µg/mL	Median Infusion Duration	No CVC, % (*n*/N)
Norepinephrine-specific evidence—short PIVC						
Hallengren et al., 2017 [52]	Retrospective; Sweden; IMCU	91 (79 via PIVC)	Short PIVC; NR	NR	13 h	98.7% (78/79)
Medlej et al., 2018 [10]	Prospective; Lebanon; ED	55 (50)	20G 50.9%, 18G 36.4%; antecubital 40%, hand 36.4%	32	13 h	76.4% (42/55) [b]
Lewis et al., 2019 [11]	Retrospective; USA; ICU and step-down	202 (146)	20G 74%, 22G 51%, 18G 23%; forearm 72%, antecubital 54%, hand 40% [a]	16, 32 or 64	7.5 h	54.0% (109/202) [b]
Padmanaban et al., 2020 [7]	Prospective consecutive cohort; India; ICU, ED, theatre	122 (118)	18G in 57%; external jugular 36.5%	40–80	9 h	68.0% (83/122) [b]

Table 4. *Cont.*

Study	Design; Country; Setting	*n* (NE-Exposed)	Device; Gauge; Site	NE Concentration, µg/mL	Median Infusion Duration	No CVC, % (*n*/N)
Nguyen et al., 2021 [12]	Retrospective, NE-only protocol; USA; ED	177 (177)	18G 58.2%, 20G 25.4%; antecubital 68.4%, external jugular 9.0%	64	62 min	16.4% (29/177)
Messina et al., 2021 [53]	Retrospective; Italy; ED	127 (127)	At or above antecubital fossa or external jugular; NR	80	15 h [e]	91.3% in the ED (116/127)
Ruchti et al., 2021 [48]	Prospective QI cohort, NE vs. metaraminol groups; Australia; ICU	100 (50)	Dedicated PIVC, ideally ≥18G	8	2 (IQR 1–3) [f]	76.0% (38/50)
Bima et al., 2022 [40]	Prospective, historical controls; Uganda; ED and medical ward	12 (12)	Dedicated PIVC, usually 18G; gravity drip, no pump	4–8 [g]	15 h	NA (no CVC available)
Cape et al., 2022 [50]	Prospective QI pilot, NE-only; USA; MICU	84 (84); 92 infusions	18–20G; ≥2 PIVCs; ≥5 cm above wrist	16	2.95 h	33.7% (31/92 infusions)
Groetzinger et al., 2022 [51]	Pilot protocol, retrospective review; USA; MICU	87 (87)	18G in 53%; some ultrasound-guided	32	8.7 h	50.6% (44/87)
Marti et al., 2022 [31] [i]	Retrospective QI review of a three-month pilot; USA; three ICUs	79; 129 orders (67 NE)	Two PIVCs with brisk blood return required; NR	NR	Mean 20 h	57.0% (45/79) [b]
Fabick et al., 2023 [49]	Retrospective pre–post implementation; USA; ICUs	3430; 1340 with peripheral NE	18G 35–50%, 20G 24–39%; antecubital 32–35%, forearm 22–35%, hand 7–14% [a,l]	16	15.4 and 14.3 h [l]	36.2% and 40.5% PIVC only [b,l]
Yerke et al., 2024 [9]	Prospective protocolised cohort; USA; MICU	635 (635)	Two PIVCs 20/22G above the wrist; ultrasound 49.8%	64	5.8 h	51.6% (311/603) [c]
Dansereau et al., 2024 [32] [i]	Retrospective pre–post implementation; USA; ICUs	250; 382 adminis trations (227 NE)	Two PIVCs required; cephalic 70%, median cubital 21% of administrations	NR	14.2 h	58.4% (146/250) [b]
Yasuda et al., 2025 [18]	Post hoc analysis of a prospective cohort; Japan; 23 ICUs	1351 (70; 91 PIVCs)	22–24G in 76.7%; forearm 48.4%	50	8.8 h	NR
Zichichi et al., 2025 [42]	Retrospective multicentre; USA; ICU and ED	198 (142)	20G 47.0%, 18G 35.9%; antecubital 31.3%, metacarpal 21.2% [m]	16	10 h	55.6% (79/142)
Goh et al., 2026 [5]	Prospective protocol implementation; Singapore; ED and ICU	217 (180)	≥20G; forearm or antecubital	40	3.3 h	41.9% (91/217) [b]
Norepinephrine-specific evidence—midline catheter						
Karlsson et al., 2024 [43]	Retrospective, three IMCUs; Sweden	461 (461); 472 episodes	Midline catheter	40	21 h	79%

Table 4. *Cont.*

Study	Design; Country; Setting	*n* (NE-Exposed)	Device; Gauge; Site	NE Concentration, µg/mL	Median Infusion Duration	No CVC, % (*n*/N)
Indirect evidence (norepinephrine >50% of exposed patients)—short PIVC						
Delaney et al., 2020 [41]	Post hoc analysis of the ARISE trial; 51 centres, five countries; ED	389 PIVC initiations (75.3% initial agent)	Short PIVC; NR	NR	1.3 h (peripheral)	7.5% (29/389)
Kilian et al., 2022 [47]	Retrospective; USA; ED	34 (85.3% first agent)	18/20G (standing order); antecubital or proximal 61.9%	NR	NR	11.8% (4/34)
Asher et al., 2023 [46]	Prospective; Israel; ICCU	108 PIVC (95.4%)	20G above the wrist in all	NR	2.5 days [h]	NR
Munroe et al., 2024 [44]	Retrospective registry cohort; USA; 29 hospitals; ED and ICU	594; 400 peripheral (84.3% initial agent)	Short PIVC (midline excluded); NR	NR	NR	33.8% (135/400)
Petros et al., 2025 [8]	Prospective multicentre; Ethiopia; ED and ICU	250 (57.6%)	18G in 58.8%; forearm 42.4%	NR	2.1 days	NR
Ramanan et al., 2025 [37]	Feasibility RCT of early vs. delayed CVC insertion; Australia; ED and ICU	40 (NE initial agent in all)	≥20G, preferably 18G; antecubital fossa or other large vein	NR	11.5–13 h [j]	60.0% (24/40) [j]
Shyu et al., 2025 [45]	Retrospective multicentre; USA; 10 hospitals; ICU and ED	9493; 3734 peripheral (88.5% initial agent)	≥22G; forearm or antecubital, not hand or wrist; ultrasound preferred	16	4.0 h [k]	24.8% (926/3734)
Indirect evidence—midline catheter or devices combined						
Prasanna et al., 2021 [54]	Retrospective; USA; ICU	248 (66.5%)	Midline catheter	32	Mean 7.8 days	88.3% (219/248)
Munroe et al., 2025 [6]	Secondary analysis of the CLOVERS trial; USA; 60 hospitals	582; 490 peripheral (94.9% initial agent)	Short PIVC or midline, not separated	NR	>6 h in 68.0%	46.7% [d]

Studies are ordered by year within each group; local events are presented in Section 3.7.4 and Table S17. Median duration refers to norepinephrine infusion where reported separately. [a] Percentages of patients, as reported; more than one site or gauge per patient was possible. [b] Whole cohort, including patients receiving other agents. [c] Patients whose first norepinephrine exposure was peripheral. [d] Patients alive at 72 h who received only peripheral vasopressors (249/533). [e] Duration during the emergency department stay. [f] Unit not stated in the source. [g] One or two 2 mg vials of norepinephrine bitartrate in 500 mL. [h] Summary statistic (mean or median) not stated. [i] Pilot (December 2020–February 2021) [31] and 12-month post-implementation cohort (December 2020–November 2021) [32] of the same programme, analysed as two studies; the periods overlap, so some patients are probably included in both. [j] Median duration of vasopressor infusion in each arm (early and delayed CVC insertion); the proportion without a CVC depended partly on allocation (80%, 16/20, in the delayed-insertion arm). [k] Time of peripheral infusion, all agents (reported as central line hours saved). [l] Before and after protocol implementation, respectively; gauge and site for all peripheral lines, all agents. [m] All agents (198 patients). ARISE, Australasian Resuscitation in Sepsis Evaluation; CVC, central venous catheter; ED, emergency department; ICCU, intensive cardiac care unit; ICU, intensive care unit; IMCU, intermediate care unit; MICU, medical ICU; NA, not applicable; NE, norepinephrine; NR, not reported; PIVC, peripheral intravenous catheter; QI, quality improvement; RCT, randomised controlled trial.

3.3. Primary Studies

Table 5 shows how the drug criterion was applied to each primary study with more than one vasoactive agent.

Table 5. Application of the drug criterion to the primary studies with more than one vasoactive agent.

Study	NE Exposure (Definition Used by the Source)	Events Attributable to NE?	Decision	Classification
Padmanaban et al. [7]	96.7% (118/122 patients)	Yes: single event in a patient on NE	Included	NE-specific
Medlej et al. [10]	90.9% (50/55 patients)	Yes: all three events in patients on NE	Included	NE-specific
Goh et al. [5]	82.9% (180/217 patients)	Yes, with caution: both events on NE; co-administration NR	Included	NE-specific
Lewis et al. [11]	72.3% (146/202 patients)	Yes: events reported by agent	Included	NE-specific
Zichichi et al. [42]	71.7% (142/198 patients)	Yes: events reported by agent	Included	NE-specific
Yasuda et al. [18]	91 of 3410 PIVCs	Yes: phlebitis analysed in NE-exposed catheters	Included	NE-specific
Ruchti et al. [48]	50% (50/100; consecutive NE and metaraminol groups)	Yes: events reported by group	Included	NE-specific
Marti et al. [31]	51.9% (67/129 orders)	Yes: events reported by agent	Included	NE-specific
Fabick et al. [49]	52.2% (1340/2569 peripheral exposures by agent; patients could receive more than one agent)	Yes: events reported by agent; events during co-administration reported separately	Included	NE-specific
Dansereau et al. [32]	59.4% (227/382 administrations)	Yes: events reported by agent	Included	NE-specific
Munroe et al. [6]	94.9% (initial agent)	No	Included (>50%)	Indirect
Asher et al. [46]	95.4% (103/108 PIVC patients)	No	Included (>50%)	Indirect
Kilian et al. [47]	85.3% (first agent)	No	Included (>50%)	Indirect
Prasanna et al. [54]	66.5%	No (the single extravasation occurred during NE; other events not by agent)	Included (>50%)	Indirect
Delaney et al. [41]	75.3% (initial agent infused through the PIVC)	Not applicable: no local injury recorded	Included (>50%)	Indirect
Petros et al. [8]	57.6%	No	Included (>50%)	Indirect
Ramanan et al. [37]	100% as initial agent (40/40); seven later received adrenaline and/or vasopressin, route not reported	No	Included (>50%)	Indirect
Munroe et al. 2024 [44]	84.3% (337/400) as initial agent	No	Included (>50%)	Indirect
Shyu et al. [45]	88.5% (3303/3734) as initial agent	No	Included (>50%)	Indirect
Marques et al. [27]	41%	No	Excluded (≤50%; post hoc criterion)	Sensitivity assessment only
Stolz et al. [28]	Peripheral only: 38% (15/39); peripheral then central: agent infused peripherally not reported (155 patients)	No	Excluded (≤50% or not determinable)	Sensitivity assessment only

Table 5. *Cont.*

Study	NE Exposure (Definition Used by the Source)	Events Attributable to NE?	Decision	Classification
Spiegel et al. [29]	Not reported (vasopressors through 119 of 403 midline catheters)	One event during NE; vasopressor subgroup not reported separately	Excluded (exposure not quantified)	Contextual mention only
Gershengorn et al. [30]	Not reported (vasopressors, including dobutamine, through 287 midline catheters)	No	Excluded (exposure not quantified)	Contextual mention only

Studies in which only norepinephrine was administered peripherally [9,12,40,43,50–53] are not included in this table. Proportions are those reported by each source and refer to patients unless otherwise stated. NE, norepinephrine; NR, not reported; PIVC, peripheral intravenous catheter.

3.4. Reviews and Evidence Syntheses

The seven included evidence syntheses are characterised in Table 6.

Table 6. Characteristics of the included evidence syntheses (contextual evidence).

Synthesis	Type; Search Period; Sources	Agents and Devices	NE-Specific Data?	Main Findings
Tian et al., 2020 [14]	Systematic review with meta-analysis; inception to February 2019; 7 studies, 1382 patients	Vasopressors; short PIVC	Partial	Extravasation 3.4% (95% CI 2.5–4.7); no tissue necrosis or limb ischaemia reported
Tran et al., 2020 [15]	Systematic review with meta-analysis; to February 2020; 9 studies, 1835 patients	Vasopressors; short PIVC	No	Complications 8.6% (95% CI 3.1–21); lower in studies with a safety protocol (2.9%) than without (12%)
Owen et al., 2021 [4]	Systematic review with meta-analysis; to October 2019; 23 studies, 16,055 adults	Mostly NE; 88% of reported catheters 16–20G	Partial	Local events in adults 1.8% (95% CI 0.1–4.8; $I^2 = 93.7\%$); mostly mild; high heterogeneity
Fernández-Ginés et al., 2025 [3]	Systematic review; 2013–2023; 83 articles, including 20 protocols	NE; heterogeneous parameters	Yes, in scope; narrative	Event frequencies generally 2–5%; important methodological limitations
Chen et al., 2025 [17]	Best-evidence summary; to June 2025; 12 sources, 29 recommendations	Vasopressors; PIVC	No	Preference for forearm, ≥20G, infusion pump and dedicated line; transferability context-dependent
Wu et al., 2025 [13]	Systematic review with meta-analysis; to August 2025; 19 studies, 6852 participants	Vasopressors; short PIVC, midline and PICC aggregated	No	Extravasation 1.43%, thrombosis 1.47%, infection 0.72%; PICC associated with more thrombosis; estimates include PICCs (contextual only)
ZhangJian et al., 2026 [16]	Systematic review with meta-analysis; to December 2025; 49 studies, 33,060 catheters	Vasopressors; short PIVC and midline (PICC excluded)	Subgroup by agent	Minor adverse events 2.3% overall and 2.6% (95% CI 1.4–4.7) for NE; venous thromboembolism 1.4% with midlines; one necrosis with short PIVCs; CVC avoided in 59.7%

Syntheses are ordered by year. Because a PICC with a centrally positioned tip provides central access, the pooled estimates of Wu et al. [13] are not estimates of peripheral administration. All syntheses include studies published before 2016 and agents other than norepinephrine, and they share primary studies (Table S19); their estimates were therefore not combined with primary data. CI, confidence interval; CVC, central venous catheter; NE, norepinephrine; PICC, peripherally inserted central catheter; PIVC, peripheral intravenous catheter.

3.5. Normative Documents

The five normative documents and their main recommendations are characterised in Table 7.

Table 7. Characteristics and recommendations of the normative documents, by nature and level of transferability.

Document	Nature and Transferability	Access	Dose and Duration	Monitoring and Extravasation
Surviving Sepsis Campaign [1]	International scientific society guideline; high transferability, no technical parameters	Suggests peripheral initiation so as not to delay restoration of MAP; does not define gauge or site	Insufficient data to recommend dose or duration; norepinephrine first line in septic shock	Requires good-quality access, frequent monitoring and treatment of extravasation
Intensive Care Society [20]	Professional society guidance; moderate transferability, partly consensus-based	≥20G, arm proximal to the wrist, avoid flexion points; blood return and 5–10 mL flush; second PIVC	16 µg/mL; start at 0.05 µg/kg/min; infusion pump; maximum and duration defined locally	Regular assessment; stop, aspirate 3–5 mL, remove, mark and elevate; transition decided locally
Royal Cornwall Hospitals NHS Trust [21]	Local institutional protocol; low transferability, requires local validation	≥20G in a good-flow forearm vein; second access; dedicated line	16 µg/mL; start at 0.05, up to 0.15 µg/kg/min while CVC is placed; review at 24 h; not routinely >48 h	Continuous ECG and SpO_2; invasive blood pressure preferred; aspirate 3–5 mL; consider nitroglycerin or phentolamine
Gloucestershire Hospitals NHS Foundation Trust [19]	Local institutional protocol; low transferability, formal review overdue since 2025	≥20G, proximal to the wrist, avoid flexion and repeated punctures; second PIVC	16 µg/mL; start at 0.05 and maximum 0.15 µg/kg/min; not to be used >48 h	Site assessment every 15 min in the first hour and at least hourly thereafter; blood pressure every 3–5 min until stable
Worcestershire Acute Hospitals NHS Trust [22]	Local institutional protocol; low transferability, requires local validation	≥20G, proximal to the wrist, avoid flexion and multiple attempts; second PIVC	16 µg/mL; start at 0.05 µg/kg/min; consider CVC if flow >50 mL/h; review at 24 h	Stop, switch to a patent PIVC, aspirate 3–5 mL, remove, mark and elevate; CVC if the need persists

The three institutional protocols represent local decisions rather than recommendations for universal application. BP, blood pressure; CVC, central venous catheter; ECG, electrocardiogram; MAP, mean arterial pressure; PIVC, peripheral intravenous catheter; SpO_2, peripheral oxygen saturation.

3.6. Results of the Critical Appraisal

Among the evidence syntheses, Owen et al. [4], Wu et al. [13], ZhangJian et al. [16] and Chen et al. [17] met most of the applicable criteria; Tian et al. [14] and Tran et al. [15] had appropriate methods but now-outdated searches, and Fernández-Ginés et al. [3] showed limitations in the search strategy, the selection criteria and the appraisal of included studies. Among the primary studies, the most frequent limitations were the absence of a comparison group, insufficient control of factors that could influence the results, single-centre conduct and, in 14 studies, retrospective ascertainment of events from medical records, which may miss minor events. Prospective cohorts with protocol-defined surveillance [5,7,9,10,50] were less exposed to under-ascertainment but small or affected by incomplete protocol adherence. The operational documents presented clear recommendations but described the methods used in their development only sparsely. On AGREE II, the Surviving Sepsis Campaign performed best in the scope, stakeholder involvement and clarity domains, and least well in applicability. A summary by source group is presented in Table 8 and item-level judgements in Tables S12–S16.

Table 8. Summary of the critical appraisal, by source group.

Source Group (Instrument)	Main Strengths	Main Limitations	Implication for Interpretation
Systematic reviews with meta-analysis [4,13–16] (JBI systematic reviews)	Explicit methods, risk-of-bias assessment; subgroup analyses by agent or device [13,16]	High heterogeneity; mixed agents; pre-2016 studies; shared primary studies; PICCs pooled in [13]	Contextual estimates only; not independent corroboration
Fernández-Ginés et al. [3] and Chen et al. [17] (JBI systematic reviews)	Norepinephrine-specific scope [3]; explicit grading of recommendations [17]	Search, appraisal and synthesis not robust [3]; overlapping sources [17]	Supports operational domains; requires local validation
Prospective NE-specific cohorts [5,7,9,10,40,48,50] (JBI cohort)	Defined protocols and, in most, defined surveillance; events attributable to NE	No central comparator (relevant only to comparative safety); single centre; small samples [10,40,48,50]; incomplete protocol adherence [5,9,50]; one event of uncertain severity [9]	Feasibility under protocol; does not identify protective elements
Retrospective NE-specific cohorts [11,12,31,32,42,43,49,51–53] (JBI cohort)	Larger or multicentre samples [42,43,49]; routine practice; before–after comparison [49]	Ascertainment from records; possible or suspected events [11,12,31,49,53]; composite local events not separable into extravasation [31,32]; possible over-reporting of minor events [32]; overlapping periods [31,32]; definitions and follow-up often not reported	Frequencies may be underestimated or, for minor events, overestimated
Yasuda et al. [18] (JBI cohort)	Multicentre; time-dependent multilevel modelling	Post hoc analysis; 91 exposed catheters	Dose signal hypothesis-generating
Indirect cohorts and feasibility trial [6,8,37,41,44–47,54] (JBI cohort)	Multicentre with adjustment [6,41,44,45]; prospective [8,37,46]; central comparator [6,41,44–47]; randomised timing of CVC insertion [37]	Events not attributable to NE; devices combined [6]; local injury only partly recorded [41,44,45]; small samples [37,47]	Indirect evidence; consistent with NE-specific data
Surviving Sepsis Campaign [1] (AGREE II)	High scope, stakeholder involvement and clarity	Lower applicability; very low certainty of evidence	Recommended with caveats; no technical parameters
Intensive Care Society and NHS protocols [19–22] (JBI Policy)	Identifiable authorship and detailed operational recommendations	Development and review methods not explicit; one review overdue [19]	Parameters to be treated as local policy

Item-level judgements for each source are presented in Tables S12–S16. AGREE II, Appraisal of Guidelines for Research and Evaluation II; JBI, Joanna Briggs Institute; NE, norepinephrine; NHS, National Health Service; PICC, peripherally inserted central catheter.

3.7. Synthesis of Findings

3.7.1. Site Selection and Catheter Characteristics

Guidance documents and several studies converged on a preference for a patent, visible upper-limb vein away from flexion points, with blood return and flushing without resistance. Most documents recommended a catheter of 20G or larger, an available second access and a dedicated line [5,17,20]. In the primary studies, gauges ranged from 14G to 24G and sites included the hand, forearm, antecubital fossa, upper arm and external jugular vein (Table 4). Observational evidence did not show that any gauge or site was superior, and the cohorts were not designed to test whether these features prevent injury: Owen et al. [4] found imprecise subgroup estimates, Yasuda et al. [18] included mostly 22–24G catheters, and in Medlej et al. [10] all three events occurred with 20G catheters, a descriptive observation that

cannot be interpreted as a gauge effect; similarly, in Dansereau et al. [32], half of the events occurred in the cephalic vein, the site used for 70% of administrations, without a significant difference by site. Ultrasound was considered useful when venous access was difficult and to confirm catheter position but does not replace clinical assessment of patency [5,17]. Midline catheters were used for longer infusions in two cohorts [43,54]; their thrombotic and infectious complications are reported separately (Section 3.7.4).

3.7.2. Concentration, Dose and Duration

Concentrations used in the primary studies ranged from 4 to 80 µg/mL: 4–8 µg/mL [40], 8 µg/mL [48], 16 µg/mL [42,45,49,50], 32 µg/mL [10,51,54], 40 µg/mL [5,43], 50 µg/mL [18], 64 µg/mL [9,12], 40–80 µg/mL [7], 80 µg/mL by syringe pump [53] and 16–64 µg/mL in Lewis et al. [11]. The four British operational documents used 16 µg/mL [19–22]. Infusion pumps or syringe drivers were used in most cohorts, but in one low-resource hospital norepinephrine was infused by gravity through a dedicated catheter with a mechanical drop counter [40].

Median durations of peripheral infusion ranged from about 1 h before central access [12,41] to 21 h with midline catheters [43], and were longer in three cohorts: 2.1 days with short PIVCs in Petros et al. [8], 2.5 days in Asher et al. [46] and a mean of 7.8 days with midline catheters in Prasanna et al. [54]. In Dansereau et al. [32], administrations with an event (all agents) had a longer median duration than those without (27.0 vs. 12.6 h), and 10 of the 14 events occurred after more than 24 h, four of them beyond the 72 h limit at the same site, whereas the maximum norepinephrine dose did not differ; this unadjusted comparison does not establish a duration threshold. In Fabick et al. [49], infusion for more than 24 h, absence of ultrasound-guided placement, absence of 2-hourly site assessment and rates above the protocol limit were frequent among patients with events (all agents), but these characteristics were not compared with those of patients without events. An exploratory analysis by Yasuda et al. [18] suggested a possible increase in the risk of phlebitis above a total dose of 6 mg but did not demonstrate a linear increase in risk with dose. The SSC 2026 guideline considered the data insufficient to recommend specific values for concentration, dose or duration, or a mandatory gauge or insertion site [1].

Differences in concentration between sources do not constitute direct safety comparisons between concentrations. It was therefore not possible to identify a threshold applicable across all settings.

3.7.3. Monitoring of the Access

Monitoring of the access site was a safety measure common to all sources, although its frequency varied. Protocols specified assessments between 15 and 60 min; in the primary studies, site checks ranged from every 30 min [5], 5 min after the start and at least hourly thereafter [31], hourly [12,45] or every 2 h [9,49–51], with confirmation of blood return in three [9,50,51], to three times [7], twice [10] or once daily [46], and several studies did not report a surveillance schedule (Table S17). Sources recommend that assessment include pain, burning, oedema, pallor, erythema, reduced local temperature, change in pump pressure, absence of blood return and resistance to flushing, with documentation and immediate action when changes occur [17,19,20]. In unstable patients, the documents preferred invasive blood pressure monitoring; where this was unavailable, frequent non-invasive measurements were recommended [19,21]. These intervals reflect protocol choices; no included study compared monitoring intervals.

3.7.4. Local Adverse Events by Device

Local events are presented by attribution, device and outcome in Table 9, and the proportions of source-defined extravasation or infiltration and, separately, of composite local events are shown in Figure 3. Operational definitions, grading systems, surveillance, observation after the end of infusion and missing assessments are detailed in Table S17. Results were not pooled, and proportions are not compared directly across studies, because median infusion durations ranged from about 1 h to several days and surveillance differed.

Table 9. Local adverse events by attribution to norepinephrine, device and outcome.

Study	Unit of Analysis; Event Definition	Events/ Exposed (*n*/N)	% (Exact 95% CI) [a]	Severity and Management
Source-defined extravasation or infiltration—norepinephrine-specific, short PIVC				
Hallengren et al. [52]	Patient	0/79	0.0 (0.0–4.6)	No ischaemia or necrosis; two catheter failures (pump high-resistance alarms)
Medlej et al. [10]	Patient	2/50	4.0 (0.5–13.7)	Local erythema, one with pallor; no medical or surgical intervention
Lewis et al. [11]	Patient; confirmed or possible	4/146	2.7 (0.8–6.9)	Conservative management; no ulceration or necrosis; grades inconsistently reported
Padmanaban et al. [7]	Patient	1/118	0.8 (0.02–4.6)	INS grade 2 at 52 h (20G antecubital); conservative; no sequelae
Nguyen et al. [12]	Patient; confirmed (confirmed or possible)	4/177 (8/177)	2.3 (0.6–5.7) [4.5 (2.0–8.7)]	Phentolamine in one patient; no extremity injury
Messina et al. [53]	Patient; confirmed (confirmed or possible)	1/127 (5/127)	0.8 (0.02–4.3) [3.9 (1.3–8.9)]	Severity and management not reported
Ruchti et al. [48]	Patient; suspected	2/50	4.0 (0.5–13.7)	Monitored; no further management required
Bima et al. [40]	Patient; local reaction	0/12	0.0 (0.0–26.5)	No local reaction during infusion
Cape et al. [50]	Infusion (92 infusions, 84 patients)	3/92	3.3 (0.7–9.2)	Phentolamine in all three; no long-term complications
Groetzinger et al. [51]	Patient; infiltration	1/87	1.1 (0.03–6.2)	5 h after discontinuation; no major adverse event
Fabick et al. [49]	Patient; confirmed or suspected (including co-administration)	27/1340 (34/1340)	2.0 (1.3–2.9) [2.5 (1.8–3.5)]	All agents: 15 of 58 events confirmed; phentolamine in 14 and nitroglycerin in 2; PIVC removed in 52; no permanent limb injury or plastic surgery consultation
Yerke et al. [9]	Patient	35/635	5.5 (3.9–7.6)	INS grade 0–1, 21; grade 2, 13; one recorded grade 4 of uncertain severity [b]; no surgery
Zichichi et al. [42]	Patient	8/142	5.6 (2.5–10.8)	Topical nitroglycerin in two and terbutaline in three events; two vascular surgery consultations; no compartment syndrome or surgery
Goh et al. [5]	Patient	2/180	1.1 (0.1–4.0)	Physical measures; no tissue injury at 48 h

Table 9. *Cont.*

Study	Unit of Analysis; Event Definition	Events/ Exposed (*n*/N)	% (Exact 95% CI) [a]	Severity and Management
Composite or nonspecific local events—norepinephrine-specific, short PIVC (two reports of one programme with overlapping periods) [d]				
Marti et al. [31] [d]	Order (67 NE orders; 79 patients, all agents); possible local event (phlebitis, erythema, infiltration, skin blanching or oedema)	2/67	3.0 (0.4–10.4)	Not labelled as extravasation by the bedside team; no treatment; infusion continued or moved to the alternate limb
Dansereau et al. [32] [d]	Administration (227 NE administrations; 250 patients); local irritation, infiltration or phlebitis	11/227	4.8 (2.4–8.5)	Local irritation, infiltration or phlebitis; no necrosis, gangrene or amputation; phentolamine in two events (agent NR); 12 of 14 events (all agents) managed with line change and site marking only
Extravasation—norepinephrine-specific, midline catheter				
Karlsson et al. [43]	Episode (472 episodes, 461 patients)	1/472	0.2 (0.01–1.2)	Suspected; infusion stopped and catheter replaced; no symptoms or further action
Extravasation or infiltration—indirect evidence, short PIVC				
Kilian et al. [47]	Patient	0/34	0.0 (0.0–10.3)	No digital ischaemia reported
Asher et al. [46]	Patient	1/108	0.9 (0.02–5.1)	Managed conservatively; no necrosis; CVC comparator: 1/31
Petros et al. [8]	Patient	3/250	1.2 (0.2–3.5)	All after ≥5 days; one with dark discoloration not assessed before death
Shyu et al. [45]	Patient; extravasation treated with phentolamine	31/3734	0.8 (0.6–1.2)	Chart-confirmed phentolamine use; untreated infiltration not captured; one tissue necrosis requiring fasciotomy (below)
Ramanan et al. [37]	Patient; extravasation (or tissued cannula)	1/40 (5/40)	2.5 (0.06–13.2) [12.5 (4.2–26.8)]	No tissue injury; four tissued cannulas recorded separately; external leakage in two; no CVC complications (0/18 CVCs)
Skin necrosis, peripheral ischaemia or tissue necrosis requiring surgery—indirect evidence, short PIVC				
Delaney et al. [41]	Patient; skin necrosis or peripheral ischaemia	0/389	0.0 (0.0–0.9)	Extravasation not recorded
Munroe et al. 2024 [44]	Patient; skin necrosis or ischaemia	0/400	0.0 (0.0–0.9)	Extravasation not recorded; complications abstracted from records
Shyu et al. [45]	Patient; tissue necrosis requiring surgery	1/3734	0.03 (0.001–0.15)	Surgical consultation and fasciotomy after extravasation; agent not reported
Extravasation—indirect evidence, midline catheter or devices combined				
Prasanna et al. [54]	Patient; midline	1/248	0.4 (0.01–2.2)	Occurred during NE infusion
Munroe et al. [6]	Patient; PIVC or midline	3/490	0.6 (0.1–1.8)	Two grade 1, one grade 2; no ulceration or skin necrosis

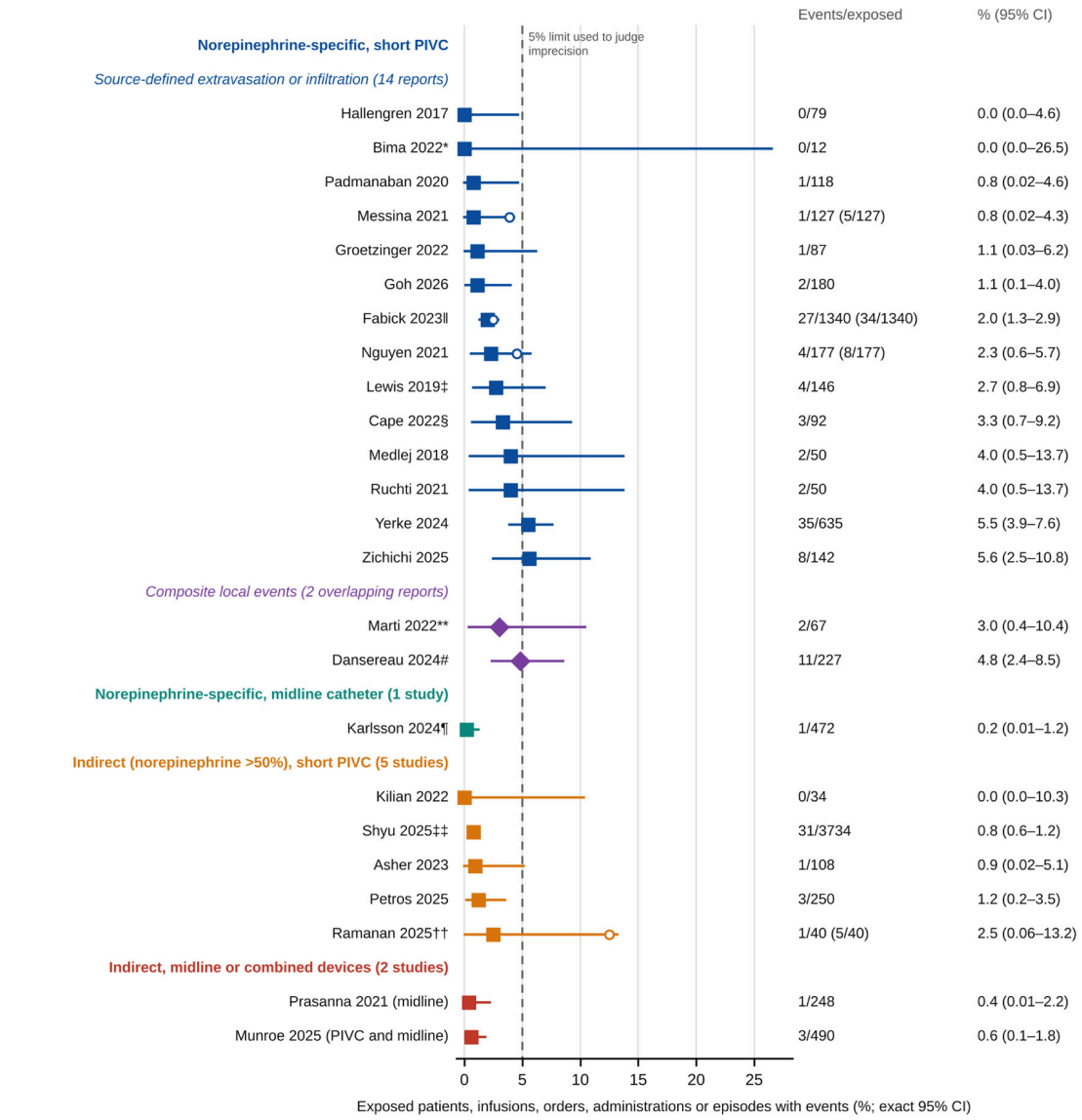
Table 9. *Cont.*

Study	Unit of Analysis; Event Definition	Events/ Exposed (*n*/N)	% (Exact 95% CI) [a]	Severity and Management
Phlebitis or thrombophlebitis				
Yasuda et al. [18]	Catheter (91 PIVCs, 70 patients); NE-specific	19/91	20.9 (13.1–30.7) [c]	Exploratory spline signal above 6 mg total dose
Medlej et al. [10]	Patient; NE-specific, PIVC	1/50	2.0 (0.05–10.6)	No intervention
Asher et al. [46]	Patient; indirect, PIVC	6/108	5.6 (2.1–11.7)	NR
Prasanna et al. [54]	Patient; indirect, midline	1/248	0.4 (0.01–2.2)	NR
Thrombosis and bloodstream infection—midline catheters				
Karlsson et al. [43]	Episode; NE-specific	Thrombosis 7/472; BSI 4/472	1.5 (0.6–3.0); 0.8 (0.2–2.2)	Four deep vein thromboses in the catheter area and three pulmonary emboli; midline-associated BSI
Prasanna et al. [54]	Patient; indirect	DVT 2/248; BSI 6/248	0.8 (0.10–2.9); 2.4 (0.9–5.2)	NR

[a] Exact (Clopper–Pearson) 95% CI calculated by the reviewers from the reported counts; values in parentheses or brackets include possible events or, for Fabick et al. [49], events during co-administration of norepinephrine with another agent; exposure-adjusted rates are given, as reported by the sources, in Table S18. [b] Site policy recorded all vasopressor extravasations as grade 4 initially; the patient died before study evaluation. [c] Crude catheter-level proportion, which does not account for several catheters per patient; the multilevel model of the source accounts for clustering. Exposure-adjusted rates were reported by five sources: 75.8 extravasations per 1000 PIVC infusion-days [9]; 33.8 per 1000 infusion-days, all agents [5]; 0.004 per patient-day [8]; 0.52 per 100 peripheral vasopressor-days [6]; and, with midline catheters, 0.08 extravasations per 1000 norepinephrine-hours, 2.2 thromboses per 1000 midline-days and 1.3 bloodstream infections per 1000 catheter-days [43]. For catheter-level phlebitis, the hazard ratio for total dose was 1.06 (95% CI 0.93–1.20) in a multilevel model [18]. [d] Pilot [31] and post-implementation [32] reports of one programme with overlapping periods; some patients are probably included in both, so the two proportions are not independent and their denominators should not be added. Events were recorded with bedside-team terms, were not labelled as extravasation and could not be separated into extravasation and other reactions; they are therefore not counted as extravasation or infiltration. One study that recorded only undefined local reactions and observed none [40] is retained under extravasation or infiltration because no local event of any type occurred. Studies are ordered by year within each group. BSI, bloodstream infection; CVC, central venous catheter; DVT, deep vein thrombosis; HR, hazard ratio; INS, Infusion Nurses Society; NE, norepinephrine; NR, not reported; PIVC, peripheral intravenous catheter.

With short PIVCs, source-defined norepinephrine-specific extravasation or infiltration occurred in 0.0% [40,52] to 5.6% [42] of exposed patients or infusions across 14 reports; where possible events were counted with confirmed events, the proportions were 3.9% [53] and 4.5% [12]. Composite local events that could not be separated into extravasation and other reactions were recorded in 3.0% of 67 norepinephrine orders [31] and 4.8% of 227 norepinephrine administrations [32], in two reports of the same programme with overlapping periods; these are not independent estimates. With midline catheters, one suspected extravasation occurred in 472 episodes [43]. In the indirect studies, proportions ranged from 0.0% to 2.5%; in the largest, which recorded only extravasation treated with phentolamine, the proportion was 0.8% (31/3734) [45], and the feasibility trial recorded tissued cannulas separately from extravasation in four further participants [37]. These estimates are not directly comparable: surveillance ranged from 30 min, hourly or two-hourly checks [5,9,12,31,49–51] to twice- or thrice-daily checks [7,10] or was not reported, and events were ascertained retrospectively from records in 14 studies; the observation window after the end of infusion differed or was not reported. Differences in event definitions and surveillance intensity may contribute to the range of estimates, alongside case mix, exposure duration and device characteristics; the available data do not allow the relative contribution

of these factors to be determined. Exposure-adjusted rates were reported in only five studies (Table 9, footnote; Table S18).



■ confirmed or reported events; ◆ composite local events; ○ including possible events or, in Ramanan 2025, tissued cannulas and, in Fabick 2023, events during co-administration. Studies ordered by proportion within groups; estimates not pooled. Composite events were not counted as extravasation; Marti 2022 and Dansereau 2024 are not independent.
* local reactions not defined; none observed. ‡ confirmed and possible events combined by the source. § infusion level (92 infusions, 84 patients). ¶ episode level (472 episodes, 461 patients); suspected extravasation. ** order level (67 norepinephrine orders); possible local events (phlebitis, erythema, infiltration, skin blanching or oedema). # administration level (227 norepinephrine administrations); local irritation, infiltration or phlebitis. ‖ confirmed or suspected events. †† randomised feasibility trial; tissued cannulas recorded separately. ‡‡ only extravasation treated with phentolamine recorded.
PIVC, peripheral intravenous catheter.

Figure 3. Proportion of exposed patients, infusions or episodes with source-defined extravasation or infiltration, by attribution to norepinephrine and device, and, separately, proportion of norepinephrine orders or administrations with composite local events, with exact 95% confidence intervals. Estimates are shown separately and were not pooled because of differences in definitions, surveillance and exposure time (Section 3.7.4). Two indirect cohorts that recorded only skin necrosis and peripheral ischaemia [41,44] are not included in the figure. The two composite-event reports describe overlapping periods of one programme and are not independent estimates [31,32]. The dashed line marks the 5% limit used to judge imprecision (Section 3.8). Studies shown, from top to bottom: Hallengren et al. [52], Bima et al. [40], Padmanaban et al. [7], Messina et al. [53], Groetzinger et al. [51], Goh et al. [5], Fabick et al. [49], Nguyen et al. [12], Lewis et al. [11], Cape et al. [50], Medlej et al. [10], Ruchti et al. [48], Yerke et al. [9], Zichichi et al. [42], Marti et al. [31], Dansereau et al. [32], Karlsson et al. [43], Kilian et al. [47], Shyu et al. [45], Asher et al. [46], Petros et al. [8], Ramanan et al. [37], Prasanna et al. [54] and Munroe et al. [6].

No norepinephrine-specific cohort reported an event requiring surgical intervention, tissue necrosis or amputation. In the largest mixed-agent cohort, in which norepinephrine was the initial peripheral agent in 88.5% of 3734 patients, one patient developed tissue necrosis after extravasation and required fasciotomy; the agent infused was not reported [45]. In two cohorts in which skin necrosis and peripheral ischaemia were specifically recorded, none occurred among 389 [41] and 400 [44] patients whose vasopressor infusion was initiated peripherally, and no local reactions were observed in 12 patients treated in a low-resource setting [40]; in the feasibility trial, with prospective surveillance by research staff, no tissue injury occurred among 40 participants [37]. This does not exclude serious injury. In Yerke et al. [9], one event recorded as grade 4 by the bedside nurse occurred in a patient who died under comfort care before study evaluation; because site policy recorded all vasopressor extravasations as grade 4 initially, regardless of tissue damage, this is an event of uncertain severity rather than confirmed severe injury. In Petros et al. [8], one patient presented with hand swelling and dark discoloration but died of refractory shock before the injury could be assessed. In Zichichi et al. [42], two patients required vascular surgery consultation to exclude compartment syndrome, which was not confirmed. Phentolamine was given in four events across two other cohorts [12,50], in two events, with the agent not stated, in a third [32], in 14 of 58 events (all agents) in a fourth, in which no event resulted in permanent limb injury or plastic surgery consultation [49], and in 31 patients in a mixed-agent cohort [45]. Follow-up after an event or after the end of infusion ranged from none [8] to 48 h [5,10] and 28 days through record review [6], or was not reported, and patients who died or were transferred to central access were not systematically followed, so late or deep injury may have been missed. In an excluded series of midline catheters, one extravasation during norepinephrine infusion led to plastic and vascular surgery consultation and phentolamine administration, without sequelae [29]. The frequency of serious injury therefore remains uncertain. With midline catheters, thrombosis (1.5%) and bloodstream infection (0.8%) were reported in the norepinephrine-specific cohort [43], complications that are characteristic of longer-dwelling devices and are not captured by extravasation estimates. In an excluded multicentre cohort in which the agents infused were not reported, venous thromboembolism occurred in 7.3% of patients who received vasopressors through a midline catheter [30].

Among the evidence syntheses (Table 6), pooled frequencies were 3.4% for extravasation in Tian et al. [14], 8.6% for complications in Tran et al. [15], 1.8% for local complications in adults in Owen et al. [4] and 2.6% for minor adverse events with norepinephrine in ZhangJian et al. [16], who identified a single tissue necrosis among 29,596 short PIVCs; the estimates of Wu et al. [13] include PICCs. These estimates combine agents, devices and pre-2016 studies, and the syntheses share primary studies with one another and with this review (Table S19); they therefore provide context, not independent corroboration.

3.7.5. Sensitivity Assessment

In the 14 norepinephrine-specific reports with short PIVCs, source-defined extravasation or infiltration occurred in 0.0% to 5.6% of exposed patients or infusions; restricting the synthesis to the five prospective cohorts with protocol-defined surveillance [5,7,9,10,50] yielded 0.8% to 5.5%. Counting possible events with confirmed events changed two estimates (from 2.3% to 4.5% [12] and from 0.8% to 3.9% [53]), both within that range. Counting the composite local events of the two overlapping reports of one programme [31,32] as extravasation, which was not done because their components could not be separated, would add proportions of 3.0% and 4.8%, within the range, and counting the seven events that occurred during co-administration of norepinephrine with another agent raised the estimate of Fabick et al. [49] from 2.0% to 2.5% (34/1340; 95% CI 1.8–3.5), also within the

range. The indirect studies contributed estimates of 0.0% to 2.5%. A stricter predominance threshold of 75% would remove two indirect cohorts [8,54], and a threshold of 90% a further four [41,44,45,47], without changing the range; the 90% threshold would, however, also remove the only cohort that reported an event requiring surgery [45]. Retaining the mixed-agent cohort excluded because norepinephrine accounted for 41% of the exposure, Marques et al. [27] (2/64 patients; 3.1%, exact 95% CI 0.4–10.8, reported by the source as 2.9%, 95% CI 1.0–8.7, with a Poisson-based method; soft-tissue swelling only) yielded an estimate within the range. In contrast, retaining the cohort excluded because the agent infused peripherally could not be established [28] would add higher proportions: extravasation in 12.8% (5/39; 95% CI 4.3–27.4) of patients who received peripheral vasopressors only and in 10.3% (16/155; 95% CI 6.0–16.2) of those later transitioned to central infusion, in a retrospective cohort that also recorded leakage and tissued cannulas and reported no major complication. Counting the tissued cannulas recorded separately in the feasibility trial as infiltration would likewise raise its estimate to 12.5% (5/40; 95% CI 4.2–26.8) [37]. These were the only scenarios that extended the range of minor event frequencies, which shows that these frequencies depend on event definitions, ascertainment and inclusion decisions. Analysing midline catheters separately did not change the short PIVC findings. Under every scenario, the conclusions on feasibility, on the uncertainty about serious injury and on the absence of a universal threshold were unchanged.

3.7.6. Management of Extravasation

When extravasation is suspected, the documents analysed recommended stopping the infusion immediately, disconnecting the infusion set from the catheter and initially leaving the catheter in place to aspirate 3–5 mL without flushing. Administration should be transferred to another available venous access. After aspiration, the catheter should be removed, the affected area demarcated and the limb elevated. The thermal measures specified in the protocol should be applied and the incident documented. Subcutaneous phentolamine was the most frequently cited antidote. Where it is unavailable, topical nitroglycerin or terbutaline may be considered as alternatives. Persistent pain, worsening of the affected area, changes in perfusion or suspected deep injury justify assessment by plastic surgery or by the tissue viability team [5,17,20]. In the primary studies, phentolamine was used in some events [12,32,45,49,50], topical nitroglycerin in two events in one cohort [49], and terbutaline or topical nitroglycerin where phentolamine was unavailable [42]. These measures derive from normative documents and expert consensus; their effectiveness in preventing injury was not assessed in the included studies.

3.7.7. Transition to Central Venous Access

Transition to central access was recommended when prolonged use was anticipated, when the dose exceeded the local threshold, when several incompatible drugs were required, when another indication for central access existed, when the peripheral access failed or extravasated, or when adequate monitoring could not be ensured [17,20–22].

The proportion of patients who did not require a CVC was reported in 23 primary studies with different denominators (Table 4). It ranged from 7.5% in a trial cohort in which central access was part of the usual care [41] to 98.7% in an intermediate care unit [52]; it was 16.4% in an emergency department protocol limited to 4 h [12], 51.6% in Yerke et al. [9] (311/603 patients whose first norepinephrine exposure was peripheral) and 79% of patients treated with midline catheters in Karlsson et al. [43]; in the feasibility trial, 80% of patients allocated to delayed insertion did not receive a CVC [37]. The denominator was norepinephrine-specific in some studies and included patients receiving other agents in others, and patients who did not receive a CVC were selected by clinicians. These values

should therefore be read as indicators of protocol performance in selected patients rather than as estimates of the safety of peripheral norepinephrine. The SSC 2026 guideline did not define a mandatory moment for transition, indicating that the decision should take account of the dose, anticipated duration, clinical course and available resources [1].

3.8. Confidence in Key Safety Findings

Confidence in the key safety findings is summarised in Table 10. Because these questions concern the frequency of events among exposed patients, cohort studies were considered the appropriate design and confidence in frequency estimates started at high, as in GRADE for prognosis [55]; for safety relative to central administration, a comparative question addressed by non-randomised data and by one small trial that randomised the timing of CVC insertion rather than the route, it started at low. Each domain was judged by two reviewers, and each serious concern lowered confidence by one level. Ratings were applied narratively, in the absence of pooled estimates [56]. Every rating refers to one outcome defined in the same way across the studies contributing to it, and report counts and combined denominators are given only to describe the evidence available, not as unique participants. Absence of a central comparator was treated as a limitation of the comparative question only, not as a risk of bias in estimating the frequency of events among exposed patients. Imprecision was judged from the study-level 95% CIs, not from the combined denominators. For extravasation or infiltration, which was mostly minor, it was judged against a clinically important frequency of 5% and, as an alternative, 10%; because no accepted threshold exists, both limits were chosen during peer review (Table S10, Amendment 12). Imprecision was rated serious when the intervals of the studies contributing most information included values on both sides of the limit, or when an outcome rested on a single study with few events; for outcomes without an agreed limit, it was judged from the number of events and the width of the study-level intervals. Confidence was very low for source-defined extravasation or infiltration in norepinephrine-specific reports with short PIVCs (low with the 10% limit), low for extravasation with midline catheters and for extravasation or infiltration in mixed-agent cohorts, and very low for composite local events, phlebitis, thrombotic and infectious complications of midline catheters, serious injury and safety relative to central administration.

Table 10. Structured assessment of confidence in key safety findings.

Outcome (Evidence)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Missing Evidence	Confidence
Source-defined extravasation or infiltration, NE-specific, short PIVC (14 reports; 12–1340 per report; 3235 exposures in total: patients in 13 reports, infusions in 1) [5,7,9–12,40,42,48–53]	Serious: retrospective ascertainment in 7 reports; surveillance varied or not reported; confirmed and possible events combined [11]	Serious: 0.0–5.6%; non-overlapping CIs in the two largest reports [9,49]; different definitions; higher proportions in an excluded cohort [28]	Not serious	Serious at 5%: CIs extend above 5% in 9 of 14 reports, including [9]; not serious at 10% (upper limits of the two largest reports 2.9% and 7.6%)	Not rated down (3 reports not retrieved; nursing studies possibly missed)	⊕○○○ Very low (⊕⊕○○ low at the 10% limit)

Table 10. *Cont.*

Outcome (Evidence)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Missing Evidence	Confidence
Composite or nonspecific local events, NE-specific, short PIVC (2 overlapping reports of one programme; 67 orders and 227 administrations, not independent) [31,32]	Serious: retrospective; bedside-team terms; possible over-reporting [32]	Not serious: 3.0% and 4.8%	Serious: composite outcome; extravasation not separable	Serious at 5% (CIs 0.4–10.4 and 2.4–8.5); not serious at 10% for the larger report	Not rated down	⊕○○○ Very low (⊕⊕○○ low at the 10% limit)
Extravasation, NE-specific, midline catheter (1 study; 472 episodes in 461 patients) [43]	Serious: retrospective; suspected events from records	Not applicable (single study)	Not serious	Serious: single study with one event (CI 0.01–1.2)	Not rated down	⊕⊕○○ Low
Extravasation or infiltration, indirect, short PIVC (5 studies; study denominators 34–3734 patients) [8,37,45–47]	Serious: retrospective record review [45,47]; only phentolamine-treated events recorded [45]; definitions not reported [46,47]	Not serious: 0.0–2.5%	Serious: events not attributable to NE	Not serious: CIs of the two largest studies below 5% (0.6–1.2 [45]; 0.2–3.5 [8])	Not rated down	⊕⊕○○ Low
Extravasation, indirect, midline catheter or devices combined (2 studies; 248 and 490 patients) [6,54]	Serious: retrospective record review	Not serious: 0.4% and 0.6%	Serious: events not attributable to NE; devices combined [6]	Not serious: upper limits 2.2% and 1.8%	Not rated down	⊕⊕○○ Low
Catheter-level phlebitis, NE-specific, short PIVC (1 study; 91 catheters in 70 patients) [18] [a]	Serious: post hoc analysis; crude proportion does not account for clustering	Not applicable (single study)	Serious: mostly 22–24G catheters, smaller than recommended in guidance	Serious: single study; crude CI (13.1–30.7) understates uncertainty because of clustering	Not rated down	⊕○○○ Very low
Venous thrombosis (deep vein thrombosis or pulmonary embolism) with midline catheters (2 studies; 472 episodes [43] and 248 patients [54])	Serious: retrospective	Not serious: 1.5% and 0.8%	Serious: mixed agents [54]	Serious: few events (7 and 2)	Not rated down	⊕○○○ Very low
Bloodstream infection with midline catheters (2 studies; 472 episodes [43] and 248 patients [54])	Serious: retrospective	Not serious: 0.8% and 2.4%	Serious: mixed agents [54]	Serious: few events (4 and 6)	Not rated down	⊕○○○ Very low

Table 10. *Cont.*

Outcome (Evidence)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Missing Evidence	Confidence
Serious injury: tissue necrosis, ischaemia or injury requiring surgery (27 studies, systematically recorded in few; one event [45])	Very serious: not systematically assessed; two events not evaluated before death [8,9]; short follow-up	Not assessable	Not serious	Very serious: rare events; zero-event data cannot exclude risk	Possible under-reporting	⊕○○○ Very low
Safety relative to central administration (3 cohorts; 1 feasibility trial) [6,37,41,46]	Serious: non-randomised cohorts with confounding by indication; trial unblinded, with 55% adherence to early insertion [37]	Not serious	Serious: mixed agents and devices; different outcomes recorded by route [41]; timing rather than route randomised [37]	Serious: few events; 40 trial participants [37]	Not rated down	⊕○○○ Very low

Confidence in frequency estimates started at high and in the comparative outcome at low (Section 3.8); each serious concern lowered confidence by one level and each very serious concern by two. ⊕⊕○○, low; ⊕○○○, very low. Imprecision was judged from study-level 95% CIs against a 5% limit for extravasation or infiltration, with 10% as an alternative (Section 3.8). Report counts and summed denominators describe the evidence available and are not unique participants; the pilot and post-implementation reports of one programme overlap [31,32]. [a] Patient-level thrombophlebitis in one cohort (1/50) [10] was not combined because its unit and definition differ. BSI, bloodstream infection; CI, confidence interval; NE, norepinephrine; PIVC, peripheral intravenous catheter.

4. Discussion

4.1. Main Findings

The evidence assembled indicates that peripheral administration of norepinephrine is feasible for treatment initiation and for short periods in selected critically ill adults managed within a system of prevention, early detection and response to extravasation [1,3,17]. The most consistent finding was not the identification of a single gauge, concentration or duration, but the recurrence across protocols of a common set of safeguards: a functional and visible access, an infusion pump, a dedicated line, an available second access, frequent observation, a prepared team and clear transition criteria [5,17,20]. Because these components were implemented together in uncontrolled cohorts, the evidence does not establish that any individual component prevents injury; in the only before–after comparison, extravasation (all agents) fell from 2.4% to 1.1%, as reported by the source, after implementation of a protocol, but this unadjusted comparison cannot attribute the change to any component [49]. In norepinephrine-specific reports with short PIVCs, source-defined extravasation or infiltration occurred in up to about 6% of exposed patients or infusions, and with midline catheters in 1 of 472 episodes; phlebitis was reported in about one in five exposed catheters in the only catheter-level study [18]. Serious injury was rare but not absent: no event requiring surgery was reported in norepinephrine-specific cohorts, but one fasciotomy for tissue necrosis occurred among 3734 patients in a large mixed-agent cohort [45]; serious injury was inconsistently assessed, and the absence of severe injury in smaller observational samples does not exclude rare events.

The most methodologically relevant finding of this review is the limited and heterogeneous nature of the data attributable to norepinephrine. Eighteen of the 27 primary studies, two of which are overlapping reports of one programme, allowed the adminis-

tered agent and the observed event to be linked, but they measured different outcomes, at different levels (patient, infusion, administration, episode or catheter), with different surveillance and follow-up, and none compared local events with a group receiving central administration. The present review therefore cannot provide a general estimate of the safety of peripheral norepinephrine; it describes the range of local events reported under the conditions studied, a range that was itself sensitive to event definitions and inclusion decisions (Section 3.7.5). In the nine indirect studies, the reported frequencies describe peripheral vasopressor administration in general. Existing reviews, by combining cohorts heterogeneous with respect to agent and device, produce estimates whose pharmacological and device attribution remains indeterminate.

Several features of the included cohorts may have influenced the observed frequencies. Peripheral administration was applied to patients judged suitable by clinicians; in Munroe et al. [6], patients who received only peripheral vasopressors were less severely ill at baseline and received lower norepinephrine doses than those who had a CVC placed, so the cohorts are not representative of all patients requiring vasopressors. Transition to central access, which occurred in a large proportion of patients in several cohorts (Table 4), and death, which was frequent in some cohorts [8,52], end peripheral exposure and observation before a local complication can occur or be recognised; follow-up after the end of infusion was short or not reported (Table S17), so late or deep injury may have been missed. Ascertainment through retrospective review of medical records, used in 14 studies, may also miss minor events. These mechanisms are likely to lead to underestimation, although in one retrospective cohort the authors suggested that minor events had been over-reported [32]. Conversely, structured surveillance may detect minor events that less frequent checks would miss, so higher proportions in intensively monitored cohorts do not necessarily indicate higher risk [37].

4.2. Comparison with Existing Evidence and Guidance

The findings are consistent with the low pooled frequencies reported by previous syntheses [4,14–16], which found heterogeneity and uncertainty; the estimates of Wu et al. [13] point in the same direction but include centrally positioned PICCs. ZhangJian et al. [16] also reported venous thromboembolism with midline catheters, consistent with the thrombotic and infectious events observed in the two midline cohorts of this review [43,54] and in an excluded multicentre cohort [30]. Because these syntheses share primary studies with one another and with this review (Table S19), their agreement does not constitute independent corroboration; in particular, ZhangJian et al. [16] included 26 of the 27 primary studies of this review, so the two reviews draw on largely the same evidence. They differ in that the present review separates norepinephrine-specific from mixed-agent data and short from midline catheters, does not pool proportions, and appraises the confidence in each finding and the source of each practice recommendation separately. The conditional recommendation of SSC 2026 favours peripheral initiation to avoid delays, without establishing technical parameters because the data are insufficient [1]. Institutional protocols were more prescriptive, generally using 16 µg/mL, a catheter of 20G or larger and time limits of 24–48 h [19,21,22]. By contrast, primary studies used concentrations between 4 and 80 µg/mL and reported a single event requiring surgery, in a mixed-agent cohort whose protocol used 16 µg/mL [45], while serious injury could not be assessed in two further events [8,9]. This difference shows that the values defined by protocols should be interpreted as local decisions rather than as universal thresholds derived from direct comparisons.

Five studies excluded at full-text assessment merit mention as contextual evidence. SPOTLESS-2, excluded under the pre-defined age criterion because it admitted participants from 16 years of age without separable results, described three episodes of infiltration or

catheter dislodgement in 468 participants in prehospital and retrieval settings, with no tissue injury at 24 h, a concentration of 60 µg/mL and visual assessment of the access at least every 15 min [38]. Marques et al. [27], excluded under the drug criterion specified after data extraction because norepinephrine accounted for only 41% of the exposure without separation of events by agent, reported two events in 64 participants in an emergency and intensive care service in Rwanda, with mild oedema and no progression at 48 h. Stolz et al. [28], excluded because norepinephrine was a minority agent among patients who received peripheral vasopressors only and the agent infused peripherally was not reported for the remaining patients, recorded leakage, extravasation, tissued cannulas or erythema in 41% of the peripheral-only group, with no major complication. Spiegel et al. [29], a series of 403 midline catheters inserted in an emergency department in which norepinephrine exposure was not quantified, reported one extravasation during norepinephrine infusion that required specialist consultation and phentolamine, without sequelae. Gershengorn et al. [30], excluded because the agents infused were not reported, compared 287 patients who received vasopressors through a midline catheter with 1660 who received them through a PICC in 39 Michigan hospitals: catheter-related complications were less frequent with midlines (5.2% vs. 13.4%), a difference that was not significant after adjustment, but venous thromboembolism was more frequent (7.3%; adjusted odds ratio 2.69, 95% CI 1.31–5.49), and extravasation was recorded in 2.1% of midlines used for vasopressors. These studies broaden the range of settings and definitions described; Marques et al. [27] and Stolz et al. [28] were examined in the sensitivity assessment (Section 3.7.5).

These findings concern continuous peripheral infusion of norepinephrine and should not be extrapolated to peri-intubation push-dose vasopressors, which are a different intervention not addressed by this review.

4.3. Implications for Clinical Practice

Most operational recommendations identified in this review—catheter characteristics, monitoring frequency, antidotes and criteria for transition to central access—derive from guidance documents, expert consensus and local institutional protocols rather than from comparative empirical evidence. Observational protocol cohorts show that peripheral administration is feasible when these safeguards are in place, but do not establish that a particular gauge, monitoring interval or antidote strategy prevents injury. They should therefore be understood as context-dependent practices, not as evidence-based universal recommendations. Table 11 summarises them, distinguishing for each its source and the confidence that can be placed in it. In clinical implementation, including in the Portuguese context, concentration, the available presentation, access to phentolamine, team composition and monitoring capacity should be assessed locally by pharmacy, medicine, nursing and medication safety structures. Implementation should also include education, simulation, standardised documentation, event auditing and periodic protocol review [17,20].

Table 11. Practice implications: supporting sources, type of support and confidence.

Practice	Main Sources	Type of Support	Status and Caveat
Supported by guideline recommendation and observational data			
Do not delay vasopressor initiation while awaiting central access	[1]; cohorts and trial [6,7,9,12,37,41,44,45]	Conditional guideline recommendation; observational cohorts; feasibility trial	Very low certainty (SSC 2026); feasibility shown, not equivalence with central access
Context-dependent practices (guidance, consensus and local protocols)			
Use a functioning, visible upper-limb vein away from flexion points, with blood return; short PIVC, or midline for anticipated longer use	[17–22,43,54]	Normative documents; observational data	No gauge or site shown to prevent injury; midlines carry thrombotic and infectious risks
Infusion pump, dedicated line and available second access	[17,19–22,40]	Normative documents	Expert consensus; protective effect not tested; gravity infusion with a drop counter used in one low-resource cohort [40]
Structured site surveillance with documentation	[5,7,9,10,12,19–22,31,45,46,49–51]	Normative documents; protocol cohorts	Intervals from 15 min to once daily; no interval shown to prevent injury
Pre-defined extravasation response: stop, aspirate, remove, mark and elevate; antidote available	[12,17,20–22,32,42,45,49,50]	Normative documents; case reports within cohorts	Antidote effectiveness not assessed in the included studies
Reassess the peripheral route and transition to CVC according to local criteria	[1,17,20–22,32]	Guideline; normative documents; one cohort	No validated dose or duration threshold; events associated with longer infusions in one unadjusted analysis [32]
Set concentration, dose and duration limits locally	[5,7,9–12,19,21,22,31,40,42,43,45,48–54]	Protocols and cohorts	Universal limits cannot be derived (4–80 µg/mL used); local decisions requiring validation
Education, audit and periodic protocol review	[17,20]	Normative documents	Expert consensus

Transferability depends on resources that were present in the cohorts and protocols analysed: nurse staffing sufficient to perform and document site assessments at the protocol interval, together with continuous haemodynamic monitoring and, in unstable patients, invasive blood pressure monitoring [19,21]; staff competent in assessing peripheral veins and, when access is difficult, in ultrasound-guided cannulation [5,9,17]; infusion pumps and dedicated lines; immediate availability of an extravasation kit and antidote (phentolamine, or topical nitroglycerin or terbutaline where it is unavailable) [20–22]; access to plastic surgery or tissue viability review; and the capacity to place a CVC promptly when transition criteria are met. Where these resources cannot be ensured, the event frequencies observed in the included cohorts cannot be assumed.

4.4. Limitations

This review has several limitations that should be considered when interpreting the findings. First, decisions made after study selection are potential sources of bias (Table 3). The protocol was registered after searching and selection; the drug criterion was operationalised after data extraction and its threshold specified during peer review; and the definition of peripheral access was corrected during peer review. Although the threshold was chosen on a conceptual basis and the sensitivity assessment showed that these decisions did not change the main conclusions, the range of minor event frequencies depended on the exclusion of one cohort [28] and on whether tissued cannulas were counted as infiltration in one trial [37], and the decisions were taken with knowledge of the candidate studies and cannot be regarded as prespecified. Second, the initial searches missed eligible studies: two

were identified by a reviewer, one not retrieved by the original strategy and one excluded in error at screening, and a further 20 primary studies and two syntheses were added after a corrected re-run of the PubMed search within the original date limit, renewed retrieval attempts and systematic citation searching. The search was limited to three overlapping databases, only PubMed was re-run, Embase and the Cochrane Library were not searched, a full-text limiter was applied in the EBSCOhost databases, which may have excluded eligible studies indexed in CINAHL Complete, particularly nursing studies (the unrestricted PubMed search and citation searching reduce this risk but cannot establish that no eligible study was excluded, and two of the three reports not retrieved were published in nursing journals), and the searches for normative documents were only partly documented (the number of results screened was not recorded and the targeted website and reference-list searches were not documented in detail). These restrictions reduce comprehensiveness compared with a full systematic review, and further eligible studies may exist.

Third, three reports identified in the databases were not retrieved, despite library requests and, where possible, requests to the authors (Table S6). For one of them, study-level data were available in an included synthesis: ZhangJian et al. [16] reported no major adverse event among 98 patients with short PIVCs (Table S6). These secondary data, which could not be verified against the primary report, suggest that the unretrieved reports are unlikely to change the conclusions on serious injury with short PIVCs, but their absence reduces precision and the range of settings represented. Further limitations derive from the evidence base itself. Definitions of infiltration, extravasation and other adverse events, surveillance intensity and follow-up after the end of infusion were heterogeneous, which compromises direct comparability of the frequencies, and in two overlapping reports local events were recorded only as a composite that could not be separated into extravasation and other reactions. Nine of the 27 primary studies do not report events separately by vasoactive agent, phlebitis data came mainly from a single catheter-level study, and only two cohorts used midline catheters. Some syntheses included the same primary studies; their estimates were not combined, which avoids double counting, but their agreement is not independent corroboration. The normative documents included are predominantly from the United Kingdom, which limits automatic transferability of their parameters to the Portuguese context. Finally, confidence was assessed with a structured approach informed by GRADE rather than a full GRADE assessment and was low or very low for all outcomes (Table 10); for norepinephrine-specific extravasation with short PIVCs, the rating depended on the clinically important limit used to judge imprecision.

4.5. Implications for Practice and Research

Practice should rest on a multidisciplinary protocol defining patient and access selection, the concentration used locally, review of dose and duration, use of an infusion pump and a dedicated line, availability of a reserve access, monitoring frequency, response to extravasation, and criteria for transition to CVC [17,20]. Further research should clarify the influence of dose, concentration and duration of administration, as well as the impact of this practice on the organisation of professionals' work and on patient outcomes [4,13].

Future studies should report adverse events separately by vasoactive agent and by vascular device, presenting the denominator exposed to each drug, the unit of analysis, exposure time, the definition and grading system used, the surveillance schedule and follow-up after the end of infusion. Without such reporting, the literature will continue to produce safety estimates that cannot be attributed to any vasopressor or device or compared across studies. Comparative studies of peripheral versus central administration, of short PIVCs versus midline catheters, and of individual protocol components are needed to establish relative safety.

5. Conclusions

In this rapid review, uncontrolled observational evidence suggests that peripheral administration of norepinephrine is feasible for timely initiation of vasopressor support in selected critically ill adults when it is delivered through a short peripheral or midline catheter within a protocol that includes frequent monitoring and a pre-defined response to extravasation. Norepinephrine-specific data come from 18 heterogeneous reports, two of which describe overlapping periods of one programme: with short PIVCs, source-defined extravasation or infiltration occurred in 0% to 5.6% of exposed patients or infusions in 14 reports, and with midline catheters in 1 of 472 episodes, alongside thrombotic and infectious complications; these frequencies were sensitive to event definitions, ascertainment and inclusion decisions. These data do not provide a general estimate of the safety of peripheral norepinephrine. Serious injury was rare, with one fasciotomy for tissue necrosis among 3734 patients in a mixed-agent cohort, but it was inconsistently assessed, and both its frequency and the safety of peripheral relative to central administration remain uncertain. Recommendations on catheter gauge, insertion site, monitoring interval, antidotes and transition criteria derive mainly from guidance and local protocols and should be applied as context-dependent practices; universal limits for concentration, dose and duration cannot be derived. The continued use of the peripheral route should be reassessed according to clinical course, anticipated duration, required dose and monitoring capacity, and central venous access should be considered when these conditions cannot be ensured.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/ecm3040037/s1, Supplementary File S1: Table S1: PubMed search strategy; Table S2: MEDLINE Complete search strategy (EBSCOhost); Table S3: CINAHL Complete search strategy (EBSCOhost); Table S4: Records exported and duplicates removed; Table S5: Corrected re-run of the PubMed search, 16 October 2026 (publication date limit unchanged); Table S6: Reports not retrieved, with retrieval attempts and data reported in the included syntheses; Table S7: Reports excluded after full-text assessment, with reasons; Table S8: Screening of the 49 studies included by ZhangJian et al.; Table S9: Fields included in the data extraction form; Table S10: Record of protocol amendments; Table S11: Planned versus modified methods; Table S12: JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses: evidence syntheses; Table S13: JBI Critical Appraisal Checklist for Cohort Studies: primary studies; Table S14: JBI Critical Appraisal Checklist for Textual Evidence: Policy/Consensus Guidelines: professional society guidance and institutional protocols; Table S15: AGREE II scaled domain scores for the Surviving Sepsis Campaign 2026 guideline; Table S16: Justification of the item-level judgements for the sources added during peer review; Table S17: Outcome definitions, surveillance and follow-up by study; Table S18: Exposed denominators, events, 95% confidence intervals and exposure-adjusted estimates by study; Table S19: Inclusion of the primary studies of this review in the included evidence syntheses; Supplementary File S2: Completed data extraction dataset; Supplementary File S3: Completed PRISMA 2020 checklist. References [57–64] are cited in the Supplementary Materials.

Author Contributions: Conceptualisation, B.R.S.; methodology, B.R.S. and I.R.; investigation, B.R.S. and I.R.; data curation, B.R.S.; formal analysis, B.R.S. and I.R.; writing—original draft preparation, B.R.S.; writing—review and editing, I.R. and H.J.; supervision, I.R.; validation, I.R.; project administration, B.R.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable. This review used exclusively published data and did not involve human participants or animals.

Informed Consent Statement: Not applicable.

Data Availability Statement: The search materials, data extraction form, completed extraction dataset (Supplementary File S2), critical appraisal records and the record of protocol amendments are available

in the Open Science Framework project at https://doi.org/10.17605/OSF.IO/6VH9E. No new data were created.

Acknowledgments: During the preparation of this manuscript and its revision, the authors used generative artificial intelligence tools to support the organisation of information and the writing of the text. The authors reviewed and edited all content and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

AGREE II	Appraisal of Guidelines for Research and Evaluation II
BSI	Bloodstream infection
CI	Confidence interval
CVC	Central venous catheter
ED	Emergency department
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICS	Intensive Care Society
ICU	Intensive care unit
IMCU	Intermediate care unit
INS	Infusion Nurses Society
ISMP	Institute for Safe Medication Practices
JBI	Joanna Briggs Institute
MAP	Mean arterial pressure
NE	Norepinephrine
NHS	National Health Service
OSF	Open Science Framework
PCC	Population, Concept and Context
PICC	Peripherally inserted central catheter
PIVC	Peripheral intravenous catheter
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SSC	Surviving Sepsis Campaign

References

1. Prescott, H.C.; Antonelli, M.; Alhazzani, W.; Møller, M.H.; Alshamsi, F.; Azevedo, L.C.P.; Belley-Cote, E.; De Waele, J.; Derde, L.; Dionne, J.C.; et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2026. *Intensive Care Med*. **2026**, *52*, 863–936, Correction in *Intensive Care Med*. **2026**, *52*, 1411–1413. https://doi.org/10.1007/s00134-026-08410-9. [CrossRef] [PubMed]
2. Institute for Safe Medication Practices. *ISMP List of High-Alert Medications in Acute Care Settings*; Institute for Safe Medication Practices: Horsham, PA, USA, 2024. Available online: https://www.ismp.org/recommendations/high-alert-medications-acute-list (accessed on 22 August 2026).
3. Fernández-Ginés, F.D.; Gómez Sánchez, M.T.; Sánchez Valera, M.; Tauste Hernández, B.; Garrido Ortiz, M.; Cortiñas-Sáenz, M. Administración segura de noradrenalina por vía periférica: Una revisión sistemática [Safe administration of noradrenaline by the peripheral route: A systematic review]. *Farm. Hosp*. **2025**, *49*, 46–52. [CrossRef]
4. Owen, V.S.; Rosgen, B.K.; Cherak, S.J.; Ferland, A.; Stelfox, H.T.; Fiest, K.M.; Niven, D.J. Adverse events associated with administration of vasopressor medications through a peripheral intravenous catheter: A systematic review and meta-analysis. *Crit. Care* **2021**, *25*, 146. [CrossRef]
5. Goh, E.L.; Wong, F.C.; Trang, T.T.L.; Teu, A.P.Y. Implementation of a nurse-led protocol for peripheral administration of vasoactive agents in critically ill patients: A prospective observational study. *Aust. Crit. Care* **2026**, *39*, 101600. [CrossRef]
6. Munroe, E.S.; Co, I.N.; Douglas, I.; Hyzy, R.; Khan, A.; Nelson, K.; Park, P.K.; Peltan, I.D.; Rice, T.W.; Seelye, S.; et al. Peripheral vasopressor use in early sepsis-induced hypotension. *JAMA Netw. Open* **2025**, *8*, e2529148. [CrossRef]
7. Padmanaban, A.; Venkataraman, R.; Rajagopal, S.; Devaprasad, D.; Ramakrishnan, N. Feasibility and safety of peripheral intravenous administration of vasopressor agents in resource-limited settings. *J. Crit. Care Med*. **2020**, *6*, 210–216. [CrossRef]
8. Petros, A.; Melkie, A.; Kotiso, K.S.; Kebede, D.; Oljira, C.F.; Gemechu, F.A.; Yusuf, H.; Abebe, S.; Ashagre, A.; Bekele, A.; et al. Peripheral line for vasopressor administration: Prospective multicenter observational cohort study for survival and safety. *PLoS ONE* **2025**, *20*, e0333275. [CrossRef]

9. Yerke, J.R.; Mireles-Cabodevila, E.; Chen, A.Y.; Bass, S.N.; Reddy, A.J.; Bauer, S.R.; Kokoczka, L.; Dugar, S.; Moghekar, A. Peripheral administration of norepinephrine: A prospective observational study. *Chest* **2024**, *165*, 348–355. [CrossRef]
10. Medlej, K.; Kazzi, A.A.; El Hajj Chehade, A.; Saad Eldine, M.; Chami, A.; Bachir, R.; Zebian, D.; Abou Dagher, G. Complications from administration of vasopressors through peripheral venous catheters: An observational study. *J. Emerg. Med.* **2018**, *54*, 47–53. [CrossRef]
11. Lewis, T.; Merchan, C.; Altshuler, D.; Papadopoulos, J. Safety of the peripheral administration of vasopressor agents. *J. Intensive Care Med.* **2019**, *34*, 26–33. [CrossRef]
12. Nguyen, T.T.; Surrey, A.; Barmaan, B.; Miller, S.; Oswalt, A.; Evans, D.; Dhindsa, H. Utilization and extravasation of peripheral norepinephrine in the emergency department. *Am. J. Emerg. Med.* **2021**, *39*, 55–59. [CrossRef]
13. Wu, W.; Yang, X.; Kou, L. Extravasation, thrombosis, and infection with vasopressor infusion through peripheral intravenous catheters: A systematic review and meta-analysis. *Cardiovasc. Diagn. Ther.* **2025**, *15*, 847–860. [CrossRef]
14. Tian, D.H.; Smyth, C.; Keijzers, G.; Macdonald, S.P.J.; Peake, S.; Udy, A.; Delaney, A. Safety of peripheral administration of vasopressor medications: A systematic review. *Emerg. Med. Australas.* **2020**, *32*, 220–227. [CrossRef]
15. Tran, Q.K.; Mester, G.; Bzhilyanskaya, V.; Afridi, L.Z.; Andhavarapu, S.; Alam, Z.; Widjaja, A.; Andersen, B.; Matta, A.; Pourmand, A. Complication of vasopressor infusion through peripheral venous catheter: A systematic review and meta-analysis. *Am. J. Emerg. Med.* **2020**, *38*, 2434–2443. [CrossRef]
16. ZhangJian, S.-J.; Niu, K.-Y.; Chen, C.-B.; Seak, C.-J.; Yen, C.-C. Incidence of adverse events in peripheral intravenous vasopressor use: A systematic review and meta-analysis. *JAMA Netw. Open* **2026**, *9*, e260710. [CrossRef]
17. Chen, G.; Shen, C.; Pan, C.; Gao, X.; Sun, M.; Li, X. Summary of best evidence for safe management of vasopressors through peripheral intravenous catheters. *BMC Nurs.* **2025**, *24*, 1000. [CrossRef]
18. Yasuda, H.; Rickard, C.M.; Schults, J.A.; Marsh, N.; Kashiura, M.; Kishihara, Y.; Shinzato, Y.; Amagasa, S.; Moriya, T.; Kotani, Y.; et al. Impact of noradrenaline administration dosage on the occurrence of peripheral intravenous catheter-related venous phlebitis in critically ill patients using a time-dependent multilevel Cox regression model. *Emerg. Med. Int.* **2025**, *2025*, 4457109. [CrossRef]
19. Gloucestershire Hospitals NHS Foundation Trust. *The Use of Peripheral Intravenous Infusion of Noradrenaline in Adult Critical Care Patients*; Version 1.1; Gloucestershire Hospitals NHS Foundation Trust: Cheltenham, UK, 2023. Available online: https://www.gloshospitals.nhs.uk/documents/17562/Department_of_Critical_Care_Peripheral_Noradrenaline_infusion.pdf (accessed on 26 August 2026).
20. Intensive Care Society. *Guidance for the Use of Vasopressor Agents by Peripheral Intravenous Infusion in Adult Critical Care Patients*; Version 1.1; Intensive Care Society: London, UK, 2022. Available online: https://ics.ac.uk/asset/3B607648-9292-4EC7-B913D5FCCA6F7D55/ (accessed on 26 August 2026).
21. Royal Cornwall Hospitals NHS Trust. *Peripheral Administration of Noradrenaline (pNA) Clinical Guideline*; Version 1.0; Royal Cornwall Hospitals NHS Trust: Truro, UK, 2023. Available online: https://doclibrary-rcht.cornwall.nhs.uk/GET/d10366271 (accessed on 26 August 2026).
22. Worcestershire Acute Hospitals NHS Trust. *Administration of Peripheral Vasopressors for Critically Ill Patients and Management of Extravasation*; Version 1.1; Document WAHT-CRI-033; Worcestershire Acute Hospitals NHS Trust: Worcester, UK, 2026. Available online: https://apps.worcsacute.nhs.uk/KeyDocumentPortal/Home/DownloadFile/4207 (accessed on 26 August 2026).
23. Garritty, C.; Hamel, C.; Trivella, M.; Gartlehner, G.; Nussbaumer-Streit, B.; Devane, D.; Kamel, C.; Griebler, U.; King, V.J. Updated recommendations for the Cochrane rapid review methods guidance for rapid reviews of effectiveness. *BMJ* **2024**, *384*, e076335. [CrossRef]
24. Aromataris, E.; Lockwood, C.; Porritt, K.; Pilla, B.; Jordan, Z. (Eds.) *JBI Manual for Evidence Synthesis*; JBI: Adelaide, Australia, 2024. [CrossRef]
25. Tricco, A.C.; Khalil, H.; Holly, C.; Feyissa, G.; Godfrey, C.; Evans, C.; Sawchuck, D.; Sudhakar, M.; Asahngwa, C.; Stannard, D.; et al. Rapid reviews and the methodological rigor of evidence synthesis: A JBI position statement. *JBI Evid. Synth.* **2022**, *20*, 944–949. [CrossRef]
26. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef] [PubMed]
27. Marques, C.G.; Mwemerashyaka, L.; Martin, K.; Tang, O.; Uwamahoro, C.; Ndebwanimana, V.; Uwamahoro, D.; Moretti, K.; Sharma, V.; Naganathan, S.; et al. Utilisation of peripheral vasopressor medications and extravasation events among critically ill patients in Rwanda: A prospective cohort study. *Afr. J. Emerg. Med.* **2022**, *12*, 154–159. [CrossRef]
28. Stolz, A.; Efendy, R.; Apte, Y.; Craswell, A.; Lin, F.; Ramanan, M. Safety and efficacy of peripheral versus centrally administered vasopressor infusion: A single-centre retrospective observational study. *Aust. Crit. Care* **2022**, *35*, 506–511. [CrossRef]
29. Spiegel, R.J.; Eraso, D.; Leibner, E.; Thode, H.; Morley, E.J.; Weingart, S. The utility of midline intravenous catheters in critically ill emergency department patients. *Ann. Emerg. Med.* **2020**, *75*, 538–545. [CrossRef]

30. Gershengorn, H.B.; Basu, T.; Horowitz, J.K.; McLaughlin, E.; Munroe, E.; O'Malley, M.; Hsaiky, L.; Flanders, S.A.; Bernstein, S.J.; Paje, D.; et al. The association of vasopressor administration through a midline catheter with catheter-related complications. *Ann. Am. Thorac. Soc.* **2023**, *20*, 1003–1011. [CrossRef]
31. Marti, K.; Hartley, C.; Sweeney, E.; Mah, J.; Pugliese, N. Evaluation of the safety of a novel peripheral vasopressor pilot program and the impact on central line placement in medical and surgical intensive care units. *Am. J. Health-Syst. Pharm.* **2022**, *79*, S79–S85. [CrossRef]
32. Dansereau, A.C.; Marti, K.E.; Mah, J.W.; Pugliese, N.M. Evaluation of the safety and efficacy of peripheral vasopressors to decrease central line placement and associated bloodstream infections. *J. Infect. Prev.* **2024**, *25*, 153–160. [CrossRef]
33. Ouzzani, M.; Hammady, H.; Fedorowicz, Z.; Elmagarmid, A. Rayyan—A web and mobile app for systematic reviews. *Syst. Rev.* **2016**, *5*, 210. [CrossRef] [PubMed]
34. Joanna Briggs Institute. *Critical Appraisal Tools*; Joanna Briggs Institute: Adelaide, Australia, 2025. Available online: https://jbi.global/critical-appraisal-tools (accessed on 22 August 2026).
35. AGREE Next Steps Consortium. *The AGREE II Instrument*; AGREE Next Steps Consortium: Hamilton, ON, Canada, 2017. Available online: https://www.agreetrust.org/resource-centre/agree-ii/ (accessed on 22 August 2026).
36. McArthur, A.; Cooper, A.; Edwards, D.; Klugarova, J.; Yan, H.; Barber, B.V.; Gregg, E.; Weeks, L.; Jordan, Z. Textual evidence systematic reviews series paper 3: Critical appraisal of evidence from narrative, opinion, and policy. *JBI Evid. Synth.* **2025**, *23*, 833–839. [CrossRef]
37. Ramanan, M.; Apte, Y.; Watts, S.; Holland, T.; Hatt, A.; Craswell, A.; Lin, F.; Tabah, A.; Ware, R.S.; Byrnes, J.; et al. A randomised, controlled, feasibility trial comparing vasopressors infused via peripheral cannula versus central venous access for critically ill adults: The VIPCA trial. *Crit. Care Resusc.* **2025**, *27*, 100106. [CrossRef]
38. Greaves, R.L.; Quay, A.; Bolot, R.; King, J.; Gibbs, C. Safety of peripheral vasoactive drug administration in prehospital and retrieval medicine (SPOTLESS-2): A prospective observational cohort study. *Acad. Emerg. Med.* **2026**, *33*, e70271. [CrossRef]
39. Gandotra, S.; Wunsch, H.; Bosch, N.A.; Walkey, A.J.; Teja, B. Reducing central venous catheter use through adoption of guidelines for peripheral catheter-based vasopressor delivery. *Ann. Am. Thorac. Soc.* **2023**, *20*, 1219–1223. [CrossRef]
40. Bima, P.; Orlotti, C.; Smart, O.G.; Morello, F.; Trunfio, M.; Brazzi, L.; Montrucchio, G. Norepinephrine may improve survival of septic shock patients in a low-resource setting: A proof-of-concept study on feasibility and efficacy outside the intensive care unit. *Pathog. Glob. Health* **2022**, *116*, 389–394. [CrossRef]
41. Delaney, A.; Finnis, M.; Bellomo, R.; Udy, A.; Jones, D.; Keijzers, G.; Macdonald, S.; Peake, S. Initiation of vasopressor infusions via peripheral versus central access in patients with early septic shock: A retrospective cohort study. *Emerg. Med. Australas.* **2020**, *32*, 210–219. [CrossRef]
42. Zichichi, A.; Wallace, R.; Daniell, J.; Rouse, G.; Ahearn, P.; Ammar, M. Safety of peripherally infused sympathomimetic vasopressors in the intensive care unit and emergency department. *Ann. Pharmacother.* **2025**, *59*, 397–405. [CrossRef]
43. Karlsson, H.; Afrasiabi, A.; Ohlsson, M.; Månsson, V.; Hartman, H.; Torisson, G. Treating shock with norepinephrine administered in midline catheters in an intermediary care unit: A retrospective cohort study. *BMJ Open* **2024**, *14*, e091311. [CrossRef]
44. Munroe, E.S.; Heath, M.E.; Eteer, M.; Gershengorn, H.B.; Horowitz, J.K.; Jones, J.; Kaatz, S.; Tamae Kakazu, M.; McLaughlin, E.; Flanders, S.A.; et al. Use and outcomes of peripheral vasopressors in early sepsis-induced hypotension across Michigan hospitals: A retrospective cohort study. *Chest* **2024**, *165*, 847–857. [CrossRef]
45. Shyu, D.; Ingraham, N.E.; Linke, C.A.; Siegel, L.; Larson, J.A.; Benson, A.R.; Pendleton, K.M. Overview of peripheral vasopressor use in an academic health system. *Ann. Am. Thorac. Soc.* **2025**, *22*, 1201–1209. [CrossRef]
46. Asher, E.; Karameh, H.; Nassar, H.; Yosefy, C.; Marmor, D.; Perel, N.; Taha, L.; Tabi, M.; Braver, O.; Shuvy, M.; et al. Safety and outcomes of peripherally administered vasopressor infusion in patients admitted with shock to an intensive cardiac care unit—A single-center prospective study. *J. Clin. Med.* **2023**, *12*, 5734. [CrossRef]
47. Kilian, S.; Surrey, A.; McCarron, W.; Mueller, K.; Wessman, B.T. Vasopressor administration via peripheral intravenous access for emergency department stabilization in septic shock patients. *Indian J. Crit. Care Med.* **2022**, *26*, 811–815. [CrossRef]
48. Ruchti, V.E.W.; Wibrow, B.A.; Seet, J.; Jacques, A.; Jha, N.; Anstey, M.H. A prospective comparison of peripheral metaraminol versus dilute noradrenaline in the intensive care unit. *Anaesth. Intensive Care* **2021**, *49*, 144–146. [CrossRef]
49. Fabick, A.C.; Hawn, J.M.; Barwick, K.W.; Weeda, E.R.; Goodwin, A.J.; Bell, C.M. Comparison of extravasation events related to the peripheral administration of vasopressors prior to and following implementation of an institutional protocol. *J. Am. Coll. Clin. Pharm.* **2023**, *6*, 709–717. [CrossRef]
50. Cape, K.M.; Jones, L.G.; Weber, M.L.; Elefritz, J.L. Implementation of a protocol for peripheral intravenous norepinephrine: Does it save central line insertion, is it safe? *J. Pharm. Pract.* **2022**, *35*, 347–351. [CrossRef]
51. Groetzinger, L.M.; Williams, J.; Svec, S.; Donahoe, M.P.; Lamberty, P.E.; Barbash, I.J. Peripherally infused norepinephrine to avoid central venous catheter placement in a medical intensive care unit: A pilot study. *Ann. Pharmacother.* **2022**, *56*, 773–781. [CrossRef]
52. Hallengren, M.; Åstrand, P.; Eksborg, S.; Barle, H.; Frostell, C. Septic shock and the use of norepinephrine in an intermediate care unit: Mortality and adverse events. *PLoS ONE* **2017**, *12*, e0183073. [CrossRef]

53. Messina, A.; Milani, A.; Morenghi, E.; Costantini, E.; Brusa, S.; Negri, K.; Alberio, D.; Leoncini, O.; Paiardi, S.; Voza, A.; et al. Norepinephrine infusion in the emergency department in septic shock patients: A retrospective 2-years safety report and outcome analysis. *Int. J. Environ. Res. Public Health* **2021**, *18*, 824. [CrossRef]
54. Prasanna, N.; Yamane, D.; Haridasa, N.; Davison, D.; Sparks, A.; Hawkins, K. Safety and efficacy of vasopressor administration through midline catheters. *J. Crit. Care* **2021**, *61*, 1–4. [CrossRef]
55. Iorio, A.; Spencer, F.A.; Falavigna, M.; Alba, C.; Lang, E.; Burnand, B.; McGinn, T.; Hayden, J.; Williams, K.; Shea, B.; et al. Use of GRADE for assessment of evidence about prognosis: Rating confidence in estimates of event rates in broad categories of patients. *BMJ* **2015**, *350*, h870. [CrossRef] [PubMed]
56. Murad, M.H.; Mustafa, R.A.; Schünemann, H.J.; Sultan, S.; Santesso, N. Rating the certainty in evidence in the absence of a single estimate of effect. *Evid.-Based Med.* **2017**, *22*, 85–87. [CrossRef]
57. Coyer, B.; Carlucci, M. Reducing central line utilization by peripherally infusing vasopressors. *Dimens. Crit. Care Nurs.* **2023**, *42*, 131–136. [CrossRef]
58. Mann, S.; Weaver, S.H.; Balmaceda, W.; Bobek, M.; Cardona, M.; Harvey, J.; Jones, S.; McNicholas, M.; Paliwal, M.; Prinzo, D.; et al. Peripheral vasopressor administration in adults with sepsis: A retrospective study of guideline adherence and complications. *J. Infus. Nurs.* **2026**, *49*, 13–21. [CrossRef]
59. Powell, S.M.; Faust, A.C.; George, S.; Townsend, R.; Eubank, D.; Kim, R. Effect of peripherally infused norepinephrine on reducing central venous catheter utilization. *J. Infus. Nurs.* **2023**, *46*, 210–216. [CrossRef]
60. Matthew, E. A retrospective study of the utilization of vasopressors in midline catheters. *S. D. Med.* **2022**, *75*, 453–454.
61. Stampfl, M.; DeBlieux, P. A clinical review of vasopressors in emergency medicine. *J. Emerg. Med.* **2024**, *67*, e31–e41. [CrossRef]
62. Stefanos, S.S.; Kiser, T.H.; MacLaren, R.; Mueller, S.W.; Reynolds, P.M. Management of noncytotoxic extravasation injuries. *Pharmacotherapy* **2023**, *43*, 321–337. [CrossRef]
63. Teja, B.; Bosch, N.A.; Walkey, A.J. How we escalate vasopressor and corticosteroid therapy in patients with septic shock. *Chest* **2023**, *163*, 567–574. [CrossRef]
64. Vitharana, H.S.; Amarasena, R. Study on ward-based practice of vasopressor administration for patients with sepsis. *Sri Lankan J. Anaesthesiol.* **2023**, *31*, 130–135. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.