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Systematic Review

Risk factors for infection associated with the use of external ventricular drainage: a systematic review with meta-analysis

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SUMMARY

Infection associated with the use of the external ventricular drainage (EVD) catheter in neurosurgery is linked to high morbidity and mortality, and various mechanisms are related to its occurrence. This systematic review with meta-analysis aimed to summarize and update the risk factors associated with EVD-related infection, utilizing grey literature and indexed databases. Thirty studies were included, of which nine contributed to the meta-analysis. The reported frequency of EVD-related infection varied from 1.9% to 36%, and the diagnostic criteria for infection were not standardized, with the presence of a positive culture being the most common. The primary micro-organisms identified were *Staphylococcus* spp. and *Pseudomonas* spp. Key risk factors included duration of catheterization, frequency of maintenance care, reinsertion, or number of drains. The results of the meta-analysis showed a significant effect in patients with prolonged use of EVDs, with an increase in risk of 1.47 (odds ratio) (95% confidence interval (CI) 1.03, 2.10) for each day of use (P=0.03), and showed that the number of cerebrospinal fluid collections was higher in the group with infection (P=0.00), while a greater number of EVDs used was related to a significant effect on infection rates (P=0.00), which were revealed from studies with low heterogeneity (I^2: 0%). The results indicated studies with high heterogeneity and low quality of evidence, with risk factors associated with the maintenance or management of EVD.

Introduction

The insertion of an external ventricular drainage (EVD) catheter is a frequent neurosurgical procedure for the control of acute hydrocephalus, treatment of intracranial hypertension and monitoring intracranial pressure in many diseases, such as intraventricular haemorrhage, subarachnoid haemorrhage, traumatic brain injury and bacterial meningitis [1–3].

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The use of EVDs carries a risk of healthcare-associated central nervous system (CNS) infections, these infections related to an EVD are called ventriculostomy-related infections or EVD-related infections (EVDRIs) [4], and present themselves as bacterial meningitis or ventriculitis. Ventriculitis or post-neurosurgical meningitis associated with ventriculostomy is a serious condition of various aetiologies, which leads to a worse prognosis, high morbidity and mortality, an increase in the number of days spent in intensive care units, as well as exposing the patient to possible surgical reoperations [3,5—7]. The current diagnostic gold standard is bacterial culture of the cerebrospinal fluid (CSF), however as this assay is dependent on bacterial growth rate and analysis often takes several days, empirical treatment is often initiated based on symptoms and analysis of CSF biomarkers such as leukocyte count and differential, lactate, protein, and CSF/plasma glucose ratio [4].

EVDRIs are classified as organ-space surgical site infections (SSIs) by the Centers for Disease Control and Prevention (CDC). The organ-space SSI related to the CNS can be categorized into intracranial infections (brain abscess, subdural or epidural infection, encephalitis), meningitis or ventriculitis, and spinal abscess/infection (spinal abscess and subdural spinal abscess) [8].

The number of studies investigating possible risk factors leading to EVDRI show divergent results. An integrative review published in 2002, including studies in paediatric and adult patients, pointed to an increased risk of CSF infection during the first 10 days of catheterization, as well as reporting the presence of subarachnoid haemorrhage, intraventricular haemorrhage, skull fracture with CSF leak, craniotomy, systemic infections, and catheter irrigation as risk factors for infection [9]. However, no more recent reviews were identified within a search of various databases.

Therefore, considering recent decades' technological and healthcare advances, it is worth revisiting the literature to update the potential risk factors related to EVDRI. To benefit the evaluation of patients and help health teams make decisions, this review aims to summarize and update the risk factors for infection associated with using EVDs in the adult population and, as sub-objectives, to identify the frequency of infection reported by the studies, the principal diagnostic criteria used, and the most frequently identified micro-organisms.

Methods

This systematic review with meta-analysis follows the recommendations of the Cochrane Collaboration (2019) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [10] to answer the following research question: 'What are the risk factors for the occurrence of infection associated with the use of external ventricular drainage by adult patients?'. This systematic review protocol was registered with PROSPERO under CDR (2022.306.424).

Eligibility criteria

Observational and experimental studies were included, with samples composed of adults over the age of 18 years, regardless of gender, with an EVD installed for monitoring intracranial pressure and draining CSF, and studies that did not include the diagnosis of infection associated with the use of the EVD catheter among their outcomes, and studies carried out with animal samples, *in vitro* or on mannequins, were excluded.

Research strategy

The searches were carried out in the following databases: Medline/Pubmed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Latin American and Caribbean Health Sciences Literature (LILACS), Cochrane Central Register of Controlled Trials (CENTRAL, Clinical Trials), EMBASE (Register of Controlled Trials), Scopus and Web of Science. The grey literature was accessed manually, and the Open Grey, Grey Literature Report, Google Scholar, and national thesis and dissertation databases were also searched. To locate the articles, controlled (DeCS/Mesh) and non-controlled descriptors were used, according to the specifications of each database, with no time, languages, or period restrictions (Supplementary Material A1).

Selection of studies

A total of 799 studies of possible relevance were found, and 11 records were identified through other sources. After removing duplicates, 418 studies were excluded based on reading the title and abstract. Of these, 257 studies were outside the proposed objectives, with 131 having paediatric patients in the sample, 24 being descriptive studies (series and case reports) and using six other types of devices (lumbar catheters and intraparenchymal catheters) (Figure 1).

Data extraction and quality assessment

Data extraction from the included studies was carried out independently by two reviewers, and any discrepancies between them were resolved with the participation of a third reviewer. For the extraction, a form was used with the following information: study characteristics, population characteristics, interventions and outcomes assessed.

The quality assessment of the included studies was performed using the RoB 2.0 tool for randomized clinical trials, proposed by the Cochrane Collaboration, which assesses the risk of bias in five domains: bias arising from the randomization process; bias due to deviations from the intended interventions; bias due to lack of outcome data; bias in the measurement of the outcome; and bias in the selection of the reported outcome; and we classified studies as low risk of bias, some concern and high risk of bias [11].

The risk of bias in observational studies was assessed by ROBINS-I tool, by the Cochrane Collaboration, which assesses the potential for bias in studies using seven domains, classified by time of occurrence, i.e., before the intervention (confounding bias and bias in the selection of participants), during the intervention (bias in the classification of interventions) and after the intervention (bias due to deviation from the intended interventions, bias due to missing data, bias in the measurement of outcomes, bias in the selection of reported results), using signalling questions (yes; probably yes; probably not; no and no information), classifying the studies as low, moderate, serious or critical risk of bias [12].

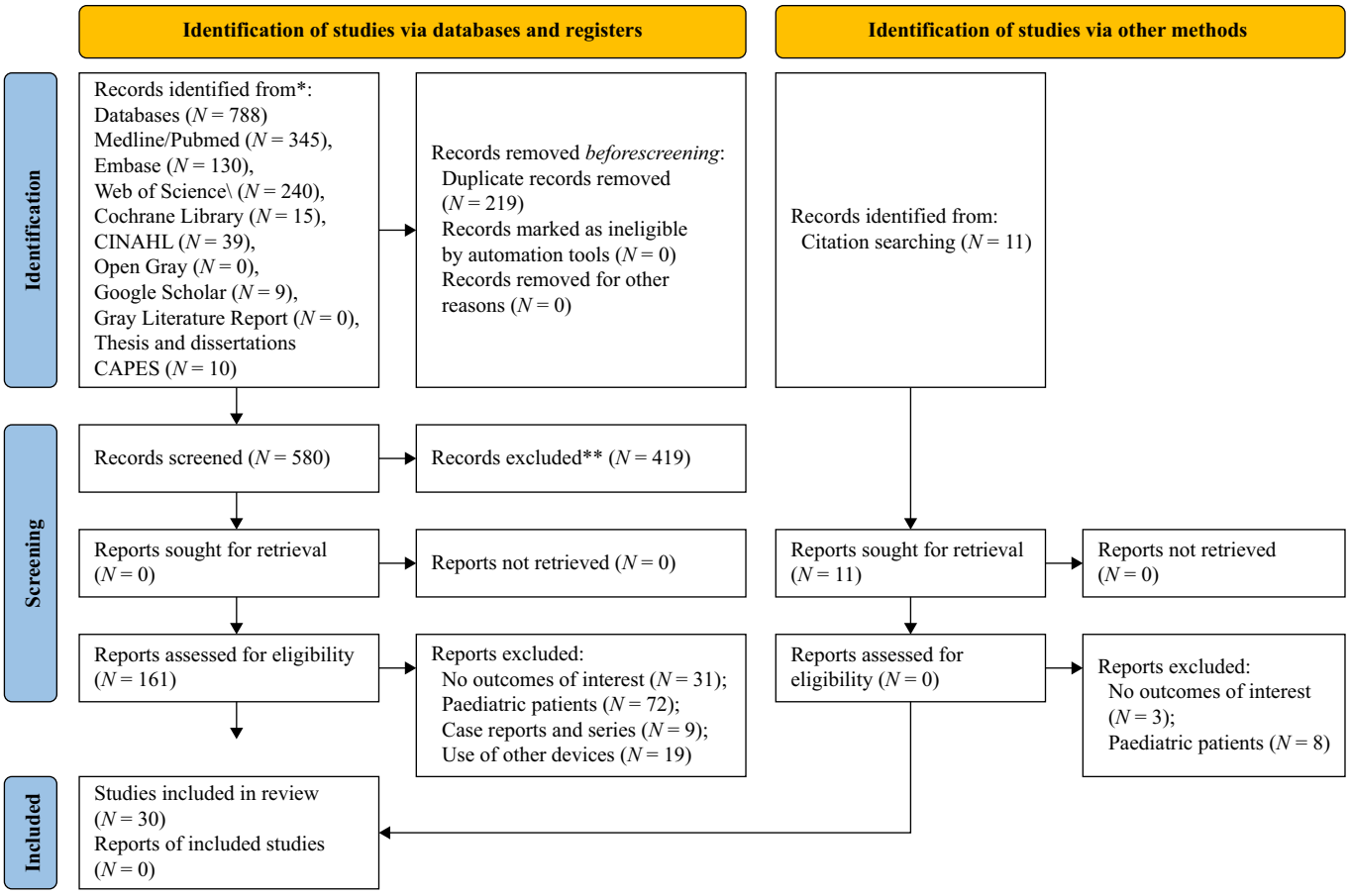

Figure 1. Flow diagram of the selection process for including studies in this review.

Assessment of the quality of evidence

The quality of the evidence was assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, considering the study design, indirect evidence, risk of bias, consistency and precision of the results and publication bias, classifying them as: high, moderate, low and very low quality [13]. The included studies were summarized descriptively, providing detailed information on each study, such as sample size, implementation and measurement of the intervention, and the main results.

The R 3.5.2 software was used to carry out the meta-analysis, adopting the random-effects model based on the logarithm of the odds ratio. Statistical significance was set at $P<0.05$.

Results

Study characteristics

This review included 30 studies that met the pre-defined selection criteria, three randomized clinical trials and 27 observational studies (five prospective cohorts, 17 retrospective cohorts and five case—control studies) (Figure 1). The studies were published between the years 2002—2022 and were written in English, with the main researchers coming from China (six) and the USA (five) (Supplementary Table A2).

Among the studies surveyed, subarachnoid haemorrhage was the clinical condition most associated with EVD use [14—26], followed by traumatic brain injury (TBI) and tumour. Intracerebral haemorrhage, intraventricular haemorrhage (IVH), cerebrovascular accident (CVA), and hydrocephalus were also conditions mentioned (Supplementary Table A2).

Main diagnostic criteria

Ten studies considered EVDRI standardized diagnostic criteria, including those proposed by the CDC between 1988 and 2021 [15,20,25—30]. Two studies applied the criteria proposed by Lozier *et al.* [9] and 19 studies determined their own criteria, including CSF contamination and related changes such as an increase in CSF protein of more than 40 g/dL, a decrease in CSF glucose of less than 45 or 50 mg/dL and pleocytosis [16,18,19,21,23,30—38]. Clinical symptoms were also assessed, mainly fever and meningeal signs (Supplementary Table A3).

Frequency of EVDRI and micro-organisms identified

The reported frequency of EVDRI varied substantially between studies, ranging from 1.9% [29] to 36% [30]. The average period for the onset of symptoms and diagnosis of infection varied between six and 36 days. The frequency of CSF culture collection varied between the studies from one to

three days, with collection in the presence of infectious signs being the most commonly used.

The main identified micro-organisms were *Staphylococcus* spp., *Pseudomonas* spp., *Acinetobacter* spp., *Enterococcus* spp. and *Klebsiella* spp.

Risk factors associated with EVDRI

Among the studies surveyed, the main risk factors identified were duration of catheterization, frequency of maintenance care, reinsertion or number of drains (Supplementary Table A4). Catheter duration appears to be potentially related to infection in nine studies [21,23,24,26—28,34,38]. The highest risk was associated with catheter permanence between five days [16] and seven days [14,39], with a progressive increase in risk for periods of 10 days or more [14,18,30], or even a progressive risk with each day of use [15]. It should also be noted that the duration of catheterization was longer in patients with infection [14,21,23—28,34,38—40].

The frequency of CSF sample collection has been identified as a risk factor [18,26,29,41], with an increased risk related to more than three collections from the same catheter [26,41] or even repeated daily collections [42]. Only one study observed that sampling or irrigating ventricular drainage systems did not increase the risk of CNS infection, provided the operator had adequate experience and used a standard aseptic technique. Five studies pointed to CSF leakage through the connection as a risk factor [19,24,28,35,37], indicating the statistically significant possibility of an increased risk if prolonged CSF leakage occurs for more than one day [35].

Other aspects mentioned in the studies, such as the indication for surgery due to a haemorrhagic event, regardless of its nature, and undergoing craniotomy [17,38], were also predisposed to the occurrence of EVDRI, or concomitant infections [25].

Quality assessment

Risk of bias of the RCTs

The assessment of the risk of bias of the RCTs which was revealed bias arising from the randomization process in one study which did not discuss randomization methods at length and was classified as 'some concerns' (Figure 2) [31]. In the case of bias due to deviations from the intended interventions, one study was classified as 'some concerns.' Another study was classified as 'some concerns' because it did not mask its sample [32]. In the case of bias in the measurement of results, one study [32] presented a high risk of bias because it was not identified that the sample had been masked, which may have generated bias in the measurement and selection of results [32].

Two studies [14,32] were classified as 'some concerns' regarding bias in the selection of the reported results: one of them registered the research protocol after the beginning of the study, there was no masking and the project was funded by the manufacturer of the EVD catheters tested [32]; the other was not reported in the study, or because it was not possible to locate the research registration protocol in the main databases, highlighting that there was no return to the consultation made with the authors until the finalization of this manuscript [14] (Figure 2).

Risk of bias of the observational studies

The risk of bias of the observational studies is described in Figure 3. A serious risk of confounding bias was identified in 19 observational studies [15—23,27—29,33—36,40,42,43], either because not all potential confounding factors (e.g., comorbidities, age, American Society of Anesthesiology (ASA) classification) were controlled for or because no information was presented to suggest that the data analysis was adjusted for these factors.

Eight studies were classified as moderate risk of bias [24—26,30,37—39,41] as all confounding domains were measured and controlled, decreasing the likelihood of a serious residual effect.

Regarding participant selection bias, 17 studies were classified as moderate to serious risk of bias [14,17,18,20—22,27,34,36—39,41—43]. Due to their retrospective designs, it was not possible to determine whether the selection of participants was free of bias, i.e., both the intervention and the outcome may be related to the selection process.

In the area of bias in the classification of interventions, observational studies with retrospective designs were judged to be at moderate risk of bias [16,18,19,23,25,27—30,39,43,44] to high [15,17,20—22,26,33,34,36,40,42], because the interventions were detailed in advance, there may be memory bias or difficulty in classifying the interventions.

In the domain of deviation from the intended interventions, four studies [16,23,30,36] were judged to be at serious risk of

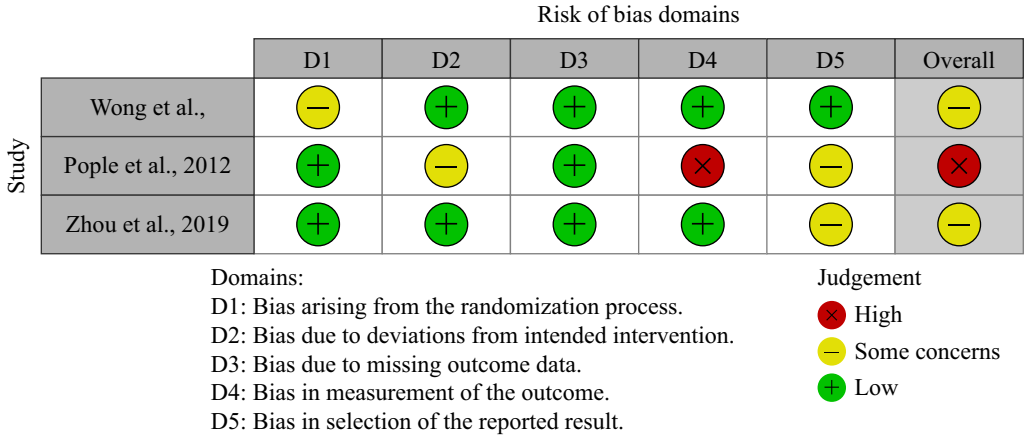

Figure 2. Assessment of the methodological quality of experimental studies.

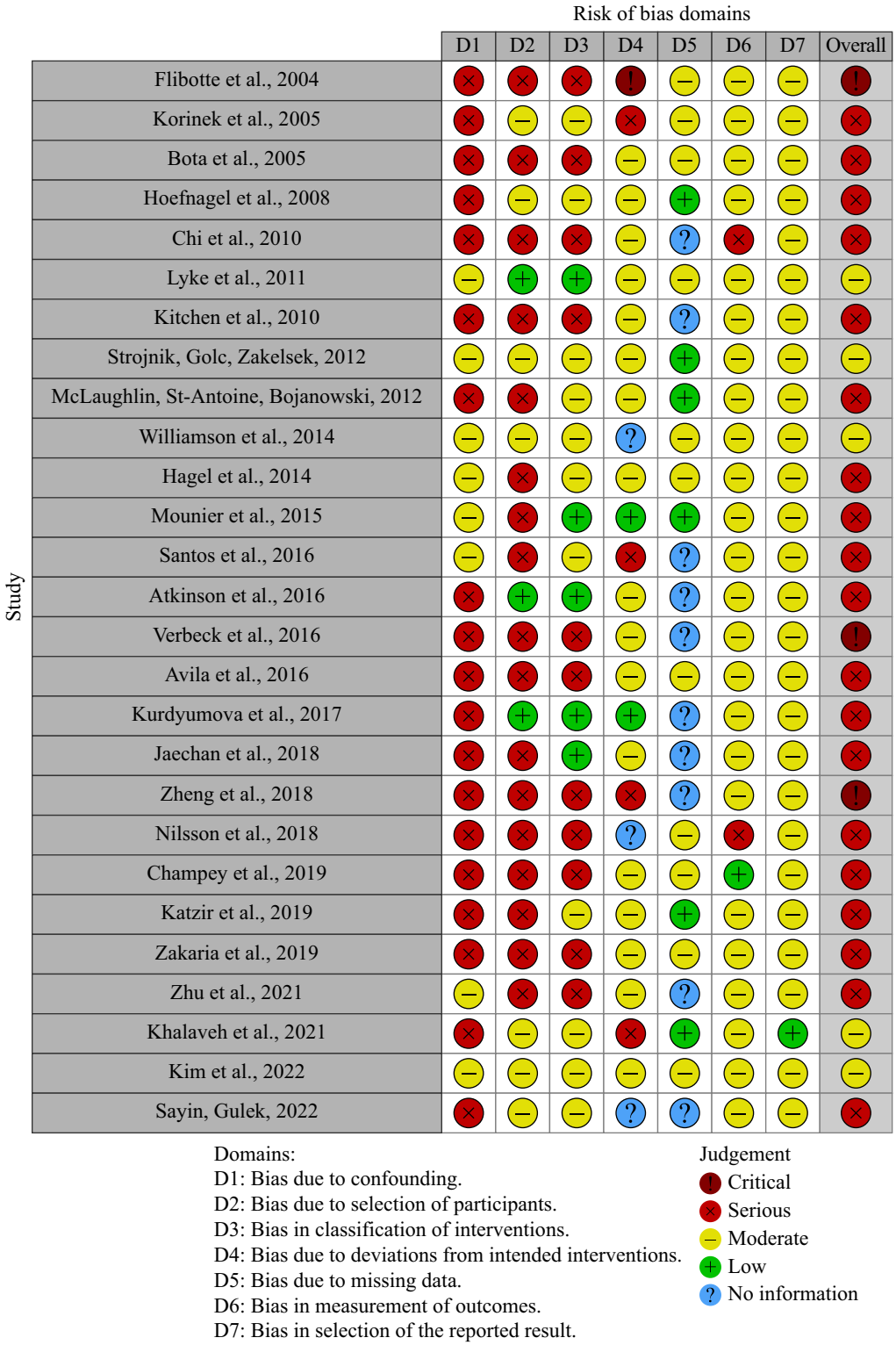

Figure 3. Assessment of the methodological quality of observational studies.

bias due to differences in the implementations of the interventions. One study [23] did not standardize antibiotic follow-up in the postoperative period, and the way CSF was sampled may have influenced the identification of cases of infection. In another analysis, the authors [16] sought to test whether establishing a strict protocol for care could reduce the number of cases of ventriculitis associated with EVD and reported difficulty in adherence and protocol violations. Two studies [30,36] showed inconsistencies in antibiotic administration, where only a few patients received antibiotic prophylaxis.

Studies that showed slight deviations in the intended interventions and did not change the outcome of the

interventions were judged to be at moderate risk of bias [17–20,22,26,27,33–36,38,40,42,43].

Studies with a retrospective design and where missing data was not addressed in the text or analyses were judged to be at moderate risk of bias due to missing data [15–17,21,22,25,34,38,39,41,42]. One study [16] was assessed as a serious risk of bias due to missing data, as the authors considered the presence of an EVD catheter for participants with missing data, and the lack of control for this factor may have interfered with the result.

In outcome measurement bias, studies in which outcome assessors were aware of participants' intervention status or outcome measurement was subjective were classified with moderate to serious risk of bias [15–21,23–30,33–43].

Finally, in terms of bias in the selection of the reported result, studies where there was no suspicion of a report of selection of the reported analysis among multiple analyses, were considered to have a moderate risk of bias [15–18,20,21,24–30,33–39].

Metanalysis

The studies that provided sufficient statistical information were included in the meta-analyses. Figure 4 shows a meta-analysis model comparing the duration of catheterization between the intervention (with infection) and control (without infection) groups. The test shows a marked effect in patients with prolonged use of EVDs, with an increase in risk of 1.47 (odds ratio, OR) for each day of use. The analysis shows high heterogeneity (I^2: 84%, $P<0.01$) between the studies and that the length of catheterization favours the occurrence of EVDRI ($P=0.03$).

Figure 5 shows the CSF frequency collection when assessing the risk of EVDRI. There was evidence of high heterogeneity between the studies (I^2: 70%, $P=0.07$), and the number of samples was higher in the intervention group, i.e., the group with EVDRI. The effect can be considered positive ($P=0.00$), i.e., the higher number of samples is related to the occurrence of infection.

Finally, Figure 6 shows an analysis model associating the number of EVD catheters used and their association with the occurrence of infection. There is a marked effect on infection rates as the number of devices used increases, and the effect can be considered significant ($P= 0.00$), with low heterogeneity (I^2: 0%, $P=0.67$).

Regarding the assessment of the quality of the evidence regarding the risk factors associated with infection, it can be seen that the certainty of the evidence can be considered low due to the downgrade observed in the items assessed for risk of bias and inconsistency generated by the high heterogeneity observed between the studies, and imprecision, caused by the wide confidence interval, and/or small sample numbers and events (Supplementary Tables A5 and A6).

Discussion

EVDRI is a common complication of patients who require placement of an external ventricular drain [4]. In the present review, the incidence rates of EVDRI were heterogeneous, ranging from 1.9% to 36.0%, which may possibly be attributable to substantial variability in the criteria used to define EVD-associated infection.

This review extends beyond the previous review study [9] by excluding paediatric patients, thereby enabling the inclusion of studies not captured in the earlier review, which focus exclusively on risk factors in the adult population.

In general terms, the risk factors associated with EVDRI can be broadly categorized into four groups: risk factors associated with the patient, the underlying mechanism of injury, the maintenance and insertion of the device and environmental influences [45]. Among them, in this analysis, the main risk factors identified by heterogenous and low-quality of evidence studies were duration of catheterization, frequency of maintenance care, reinsertion, or the number of drains, i.e., most of these factors can be considered modifiable, as they are associated with care during the handling and maintenance of the device [14–17,21–25,27–30,38–40,42,43].

It seems logical to assume that subjecting patients to a greater frequency of maintenance care and/or number of exposures predisposes them to a greater risk of developing an infection. In the analysed studies, the use of multiple EVDs, bilateral catheters and the need for reinsertions, even just one change, were associated with an increased risk of infection [29]. In addition to these conditions facilitating the access of micro-organisms to the CSF and intraventricular space [29] are the greater the number of surgical procedures, the greater the number of exposures to potential environmental contamination [46,47], or direct or indirect contact with a potentially contaminated intermediate object (e.g., bench, surgical instruments, the hand of a healthcare professional).

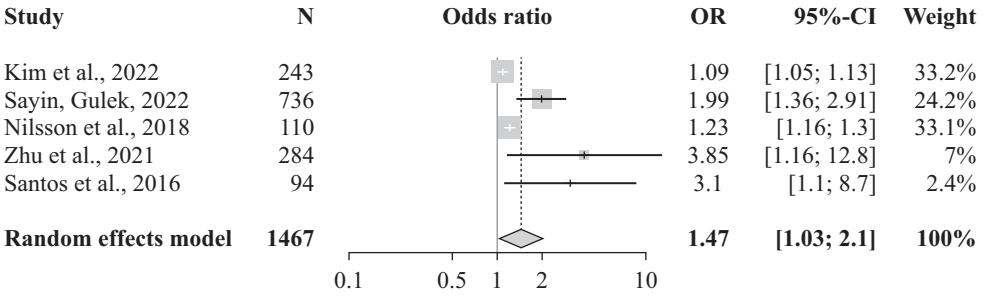

Figure 4. Meta-analysis model analysing the duration of catheterization as a risk factor for external ventricular drainage catheter-related infection in observational studies. CI, confidence interval. Heterogeneity: Tau^2: 0.317; Chi^2: 24.700, df: 4, I^2: 84%. Test for overall effect: Z = 2.1 ($P=0.03$).

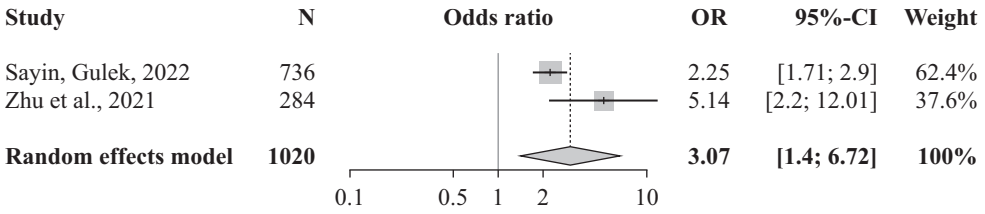

Figure 5. Meta-analysis model analysing cerebrospinal frequency collection as a risk factor for external ventricular drainage catheter-related infection in observational studies. CI, confidence interval. Heterogeneity: Tau^2: 0.488; Chi^2: 3.319, df: 1, I^2: 69.9%. Test for overall effect: Z = 2.8 (*P*=0.00).

In the same way, several authors have identified the frequency of CSF sampling as a risk factor [18,26,29,41], with an increased risk if more than three samples are collected from the same catheter [26,41], or even repeated daily collections [23], suggesting that the greater number of CSF collections is associated with an increased risk of infection [18,26,41]. In this sense, the use of appropriate aseptic techniques and adequate experience when handling the device [33], not tampering with the drainage system [48] and avoiding frequent CSF sampling is highly recommended [32].

Several studies analysed in this review have identified that CSF leaks at the insertion site significantly predispose patients to developing infection [19,22,24,35,37], increasing the risk by up to 7.33 times [24]. This condition probably favours the retrograde migration of micro-organisms to a greater extent than brief interruptions associated with the disconnection of the closed and sterile ventriculitis system, increasing the risk of infection [24,35].

Regarding the duration of use of the EVD system, it appears that periods between five and 10 days were more associated with the occurrence of EVDRI, suggesting that prolonged use of the device favours microbial colonization and a retrograde route for micro-organisms to enter the CSF and ventricular space [21,48]. In contrast, a study included in this review found that the variable duration of catheterization was not positively associated with the risk of infection, when analysing 67 patients who had catheterization duration between 10 days and 42 days, suggesting that the use of appropriate aseptic techniques and adequate experience when handling the device are important prevention measures [16].

It is worth noting that several of these mechanisms analysed separately in research, in clinical practice act together, such as with regard to the mechanism of injury, where surgical indications for haemorrhagic events, regardless of their nature, have been associated with an increased risk of SSI [17,29,39], possibly because these conditions indicate longer insertion and maintenance care times, making them more prone to contamination and infection [34].

Despite surgical duration being a known risk factor of SSI and established in various clinical guidelines [9,49], only one study in this analysis showed a positive statistical correlation with the risk of infection, demonstrating that patients with longer procedures were more likely to have the infection [44]. A meta-analysis of spinal surgery revealed a significant association between operative time of more than 3 h and SSI in neurosurgery [50], and a duration of more than 90 min doubled the risk of SSI [7]. In general, it is understood that as surgical time increases, incisions are exposed to the environment for longer, generating tissue dissection and increasing the risk of bacterial contamination [7,46,51].

Other risk factors have been identified less frequently. They may deserve to be highlighted in future investigations, such as patient characteristics and age extremes [34], with young patients showing an increased risk of 1.04 for every year of age [15]. One possible explanation for this relationship is that younger patients are more likely to undergo complex surgeries with prolonged operative times, which is an independent risk factor for SSI [52].

The results of this review reinforce the fact that the provision of quality direct care by medical and nursing professionals is a factor in preventing the occurrence of EVDRI. In this sense, several authors have shown that the implementation of a care package associated with the use of EVDs creates a 'culture of safety' and minimizes the risk of infections associated with the device [16,22,33,53,54].

A study evaluating the impact of implementing a strict care protocol to prevent EVDRI found that the average score of protocol violations showed a statistically significant difference, being four times higher in the infected group compared with the non-infected group, occurring in trichotomy, incorrect timing of asepsis, handling and use of inappropriate materials (CSF reservoir and catheter tap) [16]. Similarly, analysing frequency of CSF sampling procedures while respecting barriers such as using

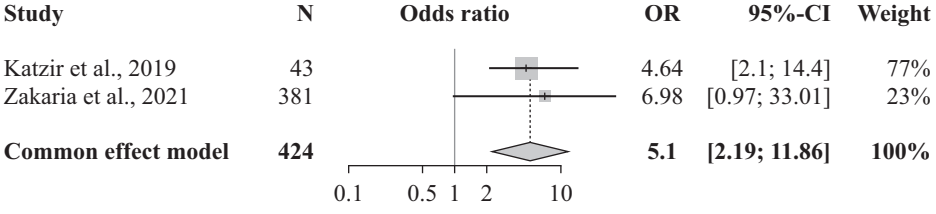

Figure 6. Meta-analysis model analysing the risk of external ventricular drainage catheter-related infection according to the number of catheters used in observational studies. CI, confidence interval. Heterogeneity: Tau^2: 0.000; Chi^2: 0.160, df: 1, I^2: 0.0% Test for overall effect: Z = 3.78 (*P*=0.00).

a face mask, sterile apron and gloves, proper hand hygiene, and a clean field resulted in a reduction in the infection rate [33]. Therefore, providing care based on the best available evidence and developing and implementing care protocols, coupled with the support of healthcare organizations, are fundamental to standardizing actions. They facilitate decision-making and provide greater safety for the team, and promote safer, high-quality and patient-centred care [55,56]. This review has some limitations. Most of the studies identified had an observational design, which may have resulted in an inherent recruitment bias, affecting the matching or pairing between two groups of patients from each individual study such that confounding factors between the study groups were not controlled, and in retrospective studies there may be recall or information bias.

In conclusion, the main risk factors observed were duration of catheterization, frequency of maintenance care, reinsertion or number of drains, i.e., the majority of these factors can be related to care during handling and maintenance of the device. The evidence from this review reinforces that the quality of direct care provided by health professionals, from device insertion to maintenance, is a preventive factor in the occurrence of EVDRI. Due to the low quality of the evidence, new, well-designed studies should be conducted to test the provision of standardized, evidence-based care and its effect on reducing EVDRI.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2024.07.004.

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