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Review paper

Risk factors for umbilical vascular catheter–related adverse events: A scoping reviewKim Gibson, MN, BN ^{a,*}Rebecca Sharp, PhD, BHSc (Hons), BN ^aAmanda Ullman, PhD, BN ^{b,e,f}Scott Morris, MBBS, PhD ^cTricia Kleidon, BN MNSci (Nurse Prac) ^{d,g}Adrian Esterman, PhD, MSc ^a^a Clinical and Health Sciences, University of South Australia, PO Box 2471, South Australia, 5000, Australia^b School of Nursing and Midwifery, Menzies Health Institute Queensland, Nathan Campus, 170 Kessels Road Queensland 4111, Australia^c College of Medicine and Public Health, Flinders University, Neonatal Unit, Flinders Medical Centre, Bedford Drive, Bedford Park, South Australia 5042, Australia^d Queensland Children's Hospital, 401 Stanley Street, South Brisbane, Q. 4101, Australia^e Children's Health Queensland and Health Service Centre of Children's Health Research, South Brisbane QLD 4101, Australia^f School of Nursing, Midwifery and Social Work The University of Queensland, Brisbane QLD 4072, Australia^g School of Nursing and Midwifery, Griffith University, 170 Kessels Raod, Nathan, Q. 4111, Australia**ARTICLE INFORMATION****Article history:**

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ABSTRACT

Introduction: Adverse events associated with umbilical catheters include malposition, bloodstream infections, thrombosis, tip migration, and extravasation, resulting in loss of vascular access and increased risk of morbidity and mortality. There is a need for greater understanding of risk factors associated with adverse events to inform safe practice.

Objectives: The aim of the study was to summarise the existing evidence regarding risk factors for umbilical catheter–related adverse events to inform the undertaking of future research.

Review method used: A scoping review of peer-reviewed original research and theses was performed.

Data sources: The US National Library of Medicine National Institutes of Health, Embase, EMcare, and ProQuest Dissertations and Theses were the data sources.

Review methods: Informed by the Joanna Briggs Institute Reviewer's Manual, all types of original research studies reporting adverse events published in English from 2009 to 2020 were eligible for inclusion. Studies where umbilical artery catheter and umbilical venous catheter data could not be extracted separately were excluded.

Results: Searching identified 1954 publications and theses, 1533 were excluded at screening, and 418 were assessed for eligibility at full text. A total of 89 studies met the inclusion criteria. A range of potential risk factors for umbilical arterial and venous catheters were identified. Longer dwell time and prematurity were associated with increased risk of bloodstream infection and thrombosis in cohort studies. Case studies detailed analogous factors such as insertion techniques and lack of catheter surveillance during dwell warrant further investigation.

Conclusions: We identified a vast range of patient, device, and provider risk factors that warrant further investigation. There was a lack of large cohort studies and randomised controlled trials to demonstrate the significance of these risk factors. Improvement in methods to ensure correct catheter tip location and

* Corresponding author.

E-mail addresses: Kim.gibson@unisa.edu.au (K. Gibson), rebecca.sharp@unisa.edu.au (R. Sharp), a.ullman@uq.edu.au (A. Ullman), Scott.Morris@sa.gov.au (S. Morris), tricia.kleidon@health.qld.gov.au (T. Kleidon), adrian.esterman@unisa.edu.au (A. Esterman).

to detect adverse events early is essential. In addition, policy needs to be developed to guide clinicians in catheter surveillance measures to reduce the risk of adverse events.

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1. Introduction

Catheterisation of the umbilical artery and vein at birth is commonly performed in the neonatal intensive care unit (NICU) shortly after birth for neonates who are premature or critically ill. Umbilical venous catheters (UVCs) provide access for administration of high-osmolarity fluid, medication, and blood products,¹ whereas umbilical arterial catheters (UACs) enable continuous monitoring of blood pressure and regular blood sample analysis for tight control of oxygenation and ventilation.²

Umbilical catheter insertion uses established landmark criteria and measurement to estimate length, such as a shoulder-to-umbilicus length graph³ or a regression equation based on birth weight (BW).⁴ Once inserted, the catheter tip location is verified using X-ray.⁵ Ideally, the UVC tip should be at the junction of the inferior vena cava and right atrium (RA), above the diaphragm, approximately at T8 to T9 on X-ray.^{6,7} The UAC is preferably placed in a 'high' position, with the catheter tip in the descending aorta above the level of the diaphragm and below the left subclavian artery.⁸ Current international recommendations⁹ endorse removing umbilical catheters as soon as possible when no longer required, using UVCs up to 14 days if managed aseptically and removing UACs within 5 days. However, umbilical catheter practice in relation to dwell time varies among Australian and New Zealand NICUs.¹⁰

Although a vital component of modern-day care in the NICU, adverse events can occur during catheter insertion or dwell time. It is common for umbilical catheters to be incorrectly positioned directly after insertion and require manipulation, which necessitates additional X-ray and radiation exposure.⁵ In addition, damage to the umbilical vessels such as pseudoaneurysm or aortic perforation can occur during difficult insertions.^{11,12}

Major adverse events during dwell include bloodstream infection (BSI) associated with central catheter use, tip migration and subsequent malposition, and thrombosis. BSI may result in increased length of stay, neurological injury, and mortality.^{13,14} Umbilical tip migration may cause damage to the surrounding tissue and organs, compounded by infusing hyperosmolar fluids causing extravasation.¹⁵ Umbilical catheters may increase the risk of thromboembolism by damaging the endothelium,^{16,17} and arterial catheter-associated thrombosis has significant local and systemic manifestations, of which a 21% mortality rate has been previously reported.¹⁸ In addition, unsuccessful catheterisation or loss of vascular access can interrupt therapy, resulting in increased mortality or neurodevelopmental impairment.²

To improve health outcomes for neonates, risk factors associated with adverse events should be identified and strategies should be implemented to minimise risk. Current international recommendations focus on limiting dwell time to reduce adverse events,⁹ yet

other variables may warrant further investigation. The aim of this scoping review was to provide a summation of existing evidence regarding all potential risk factors for umbilical catheter-related adverse events to inform the undertaking of large observational cohort studies.

2. Methods

2.1. Review framework

A scoping review is appropriate when aiming to establish the breadth of the literature available and synthesise heterogeneous research.^{19,20} An initial search of the literature indicated that a review of risk factors has not been previously published, and studies on this topic were predominately case and cohort studies. This scoping review was informed by the Joanna Briggs Institute Reviewer's Manual.²⁰ The five phases of undertaking a scoping review developed by Arksey and O'Malley¹⁹ guided this review and included; (i) identify the research question; (ii) identify relevant studies; (iii) select studies; (iv) chart the data, and (v) collate, summarise, and report the results.

2.1.1. Identify the research question

1. What are the risk factors for adverse events associated with UVCs?
2. What are the risk factors for adverse events associated with UACs?
3. What type of research evidence has been published on this topic?

2.1.2. Identify relevant studies

A systematic search was conducted seeking original research studies reporting risk factors for adverse events associated with UACs and UVCs in neonatal participants. Inclusion criteria were determined *a priori* and are outlined in Table 1. Original research including case studies was eligible for inclusion. The risk factors could be explicitly determined by the study researchers or evaluated as a potential risk factor by the review authors. The exclusion criteria were studies where risk factors were not evident or UVC and UAC data could not be extracted separately.

2.1.3. Search strategy

The search strategy and search terms were developed in consultation with an academic librarian. The Medical Subject Headings 'infant, newborn' and 'catheterisation, central venous' were used in addition to keywords 'arter* catheter*' to obtain

Table 1
Inclusion criteria.

Types of participants	Neonates (classified up to 30 days of age) ²¹ who had an UVC or UAC inserted for any length of time to capture all adverse events occurring during insertion, dwell, and removal
Concept Context	Risk factors for vascular device-related adverse events; defined as an event directly attributable to the device itself ²²
Types of evidence sources	All countries of any income or geographical location; umbilical catheters inserted and managed in the NICU or PICU using standard practices in accordance with the Infusion Therapy Standards of Practice ²³

UVC: umbilical venous catheter; UAC: umbilical arterial catheter; NICU: neonatal intensive care unit; PICU: paediatric intensive care unit.

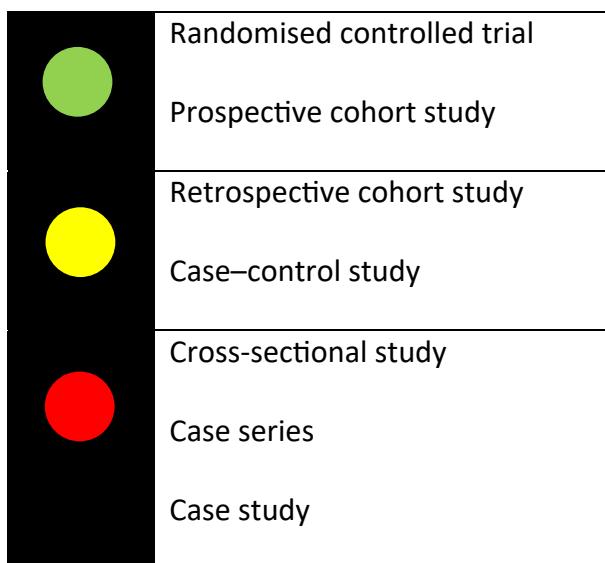


Fig. 1. The modified traffic light system for reporting the level of evidence for aetiology studies.^{26,27}

studies relating to arterial catheterisation. We applied limits to studies published in the English language from 2009 to 2020 to reflect contemporary practice. The US National Library of Medicine National Institutes of Health, Excerpta Medica dataBASE (Embase), EMcare, and ProQuest Dissertations and Theses were independently searched on April 1, 2020. The reference list of each included study was additionally hand-searched for eligible studies. Newly published articles were identified by creating an alert in Google Scholar during study screening.

2.1.4. Study selection

Studies retrieved from the databases were imported into EndNote™ (Clarivate Analytics, London, United Kingdom) and then into Covidence, Melbourne, Victoria, Australia²⁴ for screening purposes. Each phase of screening was initially conducted by the author K.G. and confirmed by either R.S. or A.U. in accordance with the predetermined inclusion criteria (Table 1). A third reviewer was used to adjudicate where there was disagreement until consensus was established.

2.1.5. Data charting

A standardised Microsoft Excel data extraction tool was completed by K.G. Extracted data included the following key information: main author, title, year of publication, country, study design, study aim, setting, participant characteristics, study results, and potential risk factors.

2.1.6. Collating, summarising, and reporting

Each study was organised in the data extraction tool in accordance with an adverse event. Types of adverse events were not determined *a priori* to remain pragmatic. The risk factors identified in each study were then categorised as either patient, device, or provider factors based on an existing conceptual model by Chopra et al.,²⁵ who investigated the patterns and predictors of adverse events associated with central venous devices in adult populations.

A traffic light system used in Cochrane reviews²⁶ was modified and implemented to map the type of study, provide a visual risk of bias, and answer research question 3. As it may only be feasible and ethical to determine a causal relationship using observational evidence, the aetiology hierarchy of evidence was used.²⁷ Level I and II evidence (randomised controlled trials [RCTs] or prospective cohort

studies) were allocated a green light. A retrospective cohort study or a case–control study (level III-2) was assigned a yellow light, and a cross-sectional study, case series, or case study (level IV) was allocated a red light (Fig. 1).^{26,27}

The Preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-SC) checklist was used to guide the reporting of this review.²⁸

3. Results

Fig. 2 details the study selection process in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.²⁹ More than 2100 studies were imported from database searching, and an additional 40 were identified from hand-searching the reference lists of the included studies. After 266 duplicates were removed, 1954 abstracts were screened and deemed irrelevant. A total of 418 were evaluated at full-text review, with a total of 89 studies included in the review.

3.1. Characteristics of the included studies

Of the 89 studies included in the review, 57 (64%) were case studies, 16 (18%) were retrospective cohort studies, 13 (15%) were prospective cohort studies, one was a pre–post intervention study, one was an RCT, and one was a non-RCT. The clinical sites were either NICUs or paediatric intensive care units.

3.2. Description of adverse events

BSI associated with umbilical catheter use was one of the major adverse events identified in the literature. There was a range of definitions used for BSI and studies detailing cases of BSI in accordance with the following criteria: central line-associated bloodstream infection (CLABSI) as per international guidelines,³⁰ defined as a primary BSI in a patient who had a central line within the 48-h period before the development of the BSI and which is not related to an infection at another site;^{31–39} (CABSI), defined as the presence of bacteria or fungi in one or more blood cultures obtained from a symptomatic infant after 2 days of placement of a central catheter or within a 48-h period after catheter removal;^{40–42} and catheter-related septicæmia, defined as clinical manifestations (clinical symptoms plus laboratory findings) and >one positive blood culture for definite pathogens or >one positive culture for other organisms, with a catheter in place.^{43–46}

Other adverse events were catheter-associated thrombosis diagnosed by radiography^{16,34,40,47–60} or by clinical signs suggestive of thrombosis,^{61,62} malposition of the catheter, with the correct position for UVCs defined as between T9 and T10 on radiography or at the inferior vena cava–RA junction^{7,47,52,54,63–84,87,92} and at T6–T10 for UACs,³⁴ migration of the catheter after the initial correct position determined via radiography or ultrasonography; extravasation of fluid from the vessel into the tissue;⁸⁵ iatrogenic events associated with insertion such as direct damage to the umbilical vessels; and necrotising enterocolitis (NEC), an inflammatory disease in the bowel in newborns based on the presence of pneumatosis (grade II or higher).⁸⁶

3.2.1. BSIs associated with catheter use

Possible risk factors for BSIs associated with UVCs and UACs are presented in Table 2. Prematurity and low birth weight (LBW) were identified as the main risk factors for BSIs associated with UVCs in three prospective and four retrospective cohort studies.^{35–37,39,41,43,46} In the study by Brito et al.,⁴³ neonates weighing ≤750 g had an UVC-related BSI rate of 3.3 per

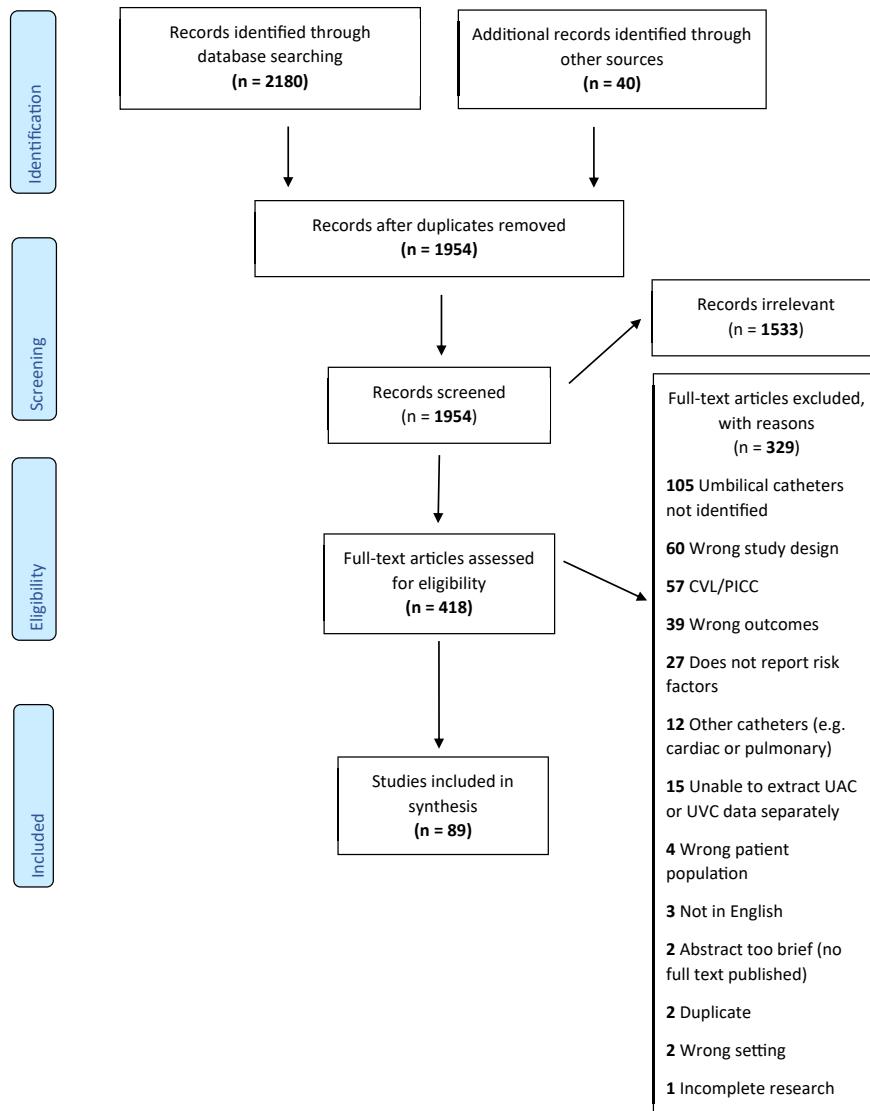


Fig. 2. PRISMA flowchart of articles screened for inclusion in the scoping review.²⁹ CVL: central venous line; PICC: peripherally inserted central catheter; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; UAC: umbilical arterial catheter; UVC: umbilical venous catheter.

1000 central venous catheter (CVC) days compared with 2.5 per 1000 CVC days for neonates weighing ≥ 2500 g. Similarly, Sanderson et al.³⁷ reported an UVC-related BSI rate of 3.3 per 1000 catheter days and that increasing gestational age was protective against the development of a BSI (hazard ratio [HR] = 1.0 95% confidence interval [CI] for 22–25 weeks versus HR = 0.20 (0.14–0.30 95% CI) for ≥ 37 weeks). Conversely, in the prospective study by Hei et al.,⁴⁵ no correlation between UVC-related BSI and BW was observed in a cohort of 285 neonates. Major congenital abnormalities placed neonates at higher risk of BSIs associated with UVCs (aHR (adjusted hazard ratio) = 1.45 (1.11–1.89 95% CI) in the retrospective study by Sanderson et al.³⁷

Butler-O'Hara et al.³² reported longer dwell time (UVC placement ≥ 7 days) to be associated with an increased risk of BSI, with an incidence rate of four UVC-related BSIs per 1000 catheter days ($p < 0.001$), compared with UVCs in place for ≤ 7 days (incidence rate of 1.0 UVC-related BSI per 1000 catheter days). When controlled for gestational age and BW, the risk of UVC-associated BSI increased over time. For UVCs *in situ* for 8–10 days, the risk of BSI was more than five times that when UVCs were in place for ≤ 7 days (RR (risk ratio) = 5.00; 95% CI = 0.98–51.00). With UVCs in

place for more than 11 days, the risk of BSI increased to more than 20 times (RR = 20.00; 95% CI = 5.00–185.00).³² Sanderson et al.³⁷ reported an increased risk of UVC-related BSI when UVCs were in place for more than 4 days, and at days 6 to 7, participants with UVCs had more than five times the risk than on days 4 to 5 (IRR = 5.85; 95% CI = 1.18–28.96). Levit et al.³⁴ reported that BSI occurred at a mean dwell time of 9.8 days (range: 5–18 days). Sharma et al.⁴² reported a case of a preterm neonate receiving total parenteral nutrition (TPN) and inotropes through a malpositioned UVC for 10 days, resulting in liver abscess and a positive blood culture growth of *Candida albicans*.

Other risk factors for BSI include the effect of antibiotic-impregnated catheter material, ceasing intravenous antibiotics, double-lumen UVCs, and low-lying UVCs. In an RCT by Bertini et al.,³¹ the effect of antibiotic-coated UVC material on UVC-related BSI versus that of polyurethane was investigated (2.1 per 1000 catheter days and 25.8 per 1000 catheter days; $p = 0.001$). Furthermore, multivariate analysis demonstrated that non-impregnated catheter use and dwell time for more than 7 days increased the risk (odds ratio [OR] = 12.5; 95% CI = 2.06–75.90). Lindquist et al.⁴⁶ demonstrated an association between BSI after

Table 2

Risk factors for umbilical catheter–related BSI and risk of bias in the studies.

Risk factors	UVCs	UACs
Patient		
LBW	Brito et al.; ⁴³ Zingg et al. ³⁹ Lindquist et al.; ⁴⁶ Mutlu et al. ³⁶ Sharma et al.; ⁴² Carvajal-Barrios et al. ⁴⁴	Lindquist et al. ⁴⁶ Hapnes et al. ⁴⁰
Prematurity	Lindquist et al.; ⁴⁶ Sanderson et al.; ³⁷ Mutlu et al.; ³⁶ McMullan and Gordon; ³⁵ Shalabi et al. ⁴¹ Sharma et al.; ⁴² Carvajal-Barrios et al. ⁴⁴	Lindquist et al. ⁴⁶ Hapnes et al. ⁴⁰
Congenital abnormality	Sanderson et al. ³⁷	
Device		
Longer dwell time (>5 days)	Brito et al.; ⁴³ Vachharajani et al.; ³⁸ Levit et al.; ³⁴ Zingg et al. ³⁹ Butler-O'Hara et al.; ³² Sanderson et al.; ³⁷ Bertini et al.; ³¹ Mutlu et al. ³⁶ Sharma et al. ⁴²	Hapnes et al. ⁴⁰
Catheter material (antibiotic)	Bertini et al. ³¹	
Hyperosmolar fluid	Zingg et al. ³⁹ Carvajal-Barrios et al. ⁴⁴	
Low-lying	El Ters et al. ³³	
Malposition and hyperosmolar fluid	Sharma et al.; ⁴² Ihm et al. ⁵⁷	
Provider		
Ceasing antibiotics upon removal	Lindquist et al. ⁴⁶	Lindquist et al. ⁴⁶

BSI: bloodstream infection; LBW: low birth weight; UVC: umbilical venous catheter; UAC: umbilical arterial catheter.

elective withdrawal of umbilical catheters without continuing antibiotics among neonates with a BW of ≤ 1500 g ($p \leq 0.001$). In addition, low-lying UVCs were associated with an UVC-related BSI relative risk ratio (RR) of 2.3 in comparison with higher positions (95% CI = 0.5–9.2, $p = 0.2$).³³

Only two studies that investigated risk factors for UAC-associated BSI could be identified. In a case study by Hapnes⁴⁰, a very low birth-weight neonate developed *Enterococcus faecium* with a presumed infected intra-aortic thrombus, after a UAC had been inserted for 9 days. Cessation of antibiotics concurrent with UAC removal was associated with the development of BSI within 72 h in one very-low-birth-weight neonate in the study by Lindquist et al.⁴⁶

3.2.2. Umbilical catheter–associated thrombosis

A total of 19 studies reported a broad range of possible risk factors for umbilical catheter–associated thrombosis (Table 3).^{16,34,40,47–62} Longer duration of UVC placement (>5 days) was associated with catheter thrombosis in three large cohort studies.^{34,48,49} Duration of UVC placement was significantly associated with catheter thrombosis (mean = 7.5 days in patients with catheter thrombosis versus 19.5 days in patients without catheter thrombosis, $p = 0.01$).⁴⁸ In a study of 2017 UVCs, there were three confirmed cases of UVC-associated thrombus. Diagnosis occurred later during catheter dwell at days 12, 14, and 15, respectively.³⁴ In the retrospective study by Arnts et al.,⁴⁹ thrombosis was detected in UVCs that all had an indwelling time longer than 7 days. Tip malposition (below the diaphragm) was significantly associated with a higher rate of portal vein thrombosis than a central position

(61% versus 38%, respectively, $p = 0.031$) in the prospective surveillance study by Cabannes et al.⁵¹ In 10% of neonates, intracardiac thrombosis was detected with inward migration of the UVC.⁵⁴

A haematocrit >55% in the first week of life was a significant and independent risk factor for UVC-associated thrombosis ($p = 0.0003$) in a retrospective study of 210 UVCs.⁵⁹ Although not significant, a prospective study by Cabannes et al.⁵¹ identified maternal diabetes, neonatal sepsis, NEC and a family history of thrombophilia as risk factors for UVC-associated thrombosis. Dehydration, polycythaemia, and congenital heart defects were also described as risk factors in a case series by Demirel et al.⁵³ Conversely, no relationship was observed between thrombosis and elevated serum sodium levels, septicaemia, maternal diabetes, or non-O blood groups in 25 neonates diagnosed with thromboembolism in the retrospective study by Narang et al.⁵⁹ In a retrospective study by Chen et al.,⁵² seven cases of hepatic extravasation had confirmed thrombus during routine follow-up ultrasound.

In a prospective cohort study by Ergaz et al.,¹⁶ 19 neonates who developed UAC-related thrombosis were significantly more premature ($p = 0.002$), were LBW ($p = 0.002$), and had longer UAC dwell times ($p < 0.001$) than those without thrombosis. A prospective cohort study by Levit et al.³⁴ found UACs associated with nonocclusive aortic thrombus in two neonates, which occurred after 12 days of dwell time and with another occurring after 4 days; the latter was subsequently diagnosed with thrombophilia. Studies reporting cases of arterial thrombosis in term neonates detailed a history of perinatal asphyxia or sepsis.^{50,56} Two studies found heparin had no effect on the incidence of umbilical catheter–related thrombosis in UACs ($P = 0.93$) and UVCs.^{16,60}

Table 3

Risk factors for umbilical catheter-associated thrombosis and risk of bias in the studies.

Risk factors	UVCS	UACs		
Patient				
LBW	● (yellow) ● (red)	Narang et al.; ⁵⁹ Chen et al. ⁵² Abiramalatha et al.; ⁴⁷ Poonai et al. ⁶²	● (green) ● (yellow) ● (red)	Ergaz et al. ¹⁶ Deindl et al. ⁶¹ Kayiran et al.; ⁵⁸ Hapnes et al. ⁴⁰
Prematurity	● (yellow) ● (red)	Chen et al. ⁵² Abiramalatha et al.; ⁴⁷ Poonai et al.; ⁶² Demirel et al. ⁵³	● (green) ● (yellow) ● (red)	Ergaz et al. ¹⁶ Deindl et al. ⁶¹ Franco et al.; ⁵⁵ Hapnes et al.; ⁴⁰ Kayiran et al. ⁵⁸
SGA	● (yellow)	Narang et al. ⁵⁹		
Maternal diabetes	● (green) ● (red)	Cabannes et al. ⁵¹ Demirel et al. ⁵³		
Maternal PE	● (yellow)	Narang et al. ⁵⁹		
Sepsis	● (green) ● (red)	Cabannes et al. ⁵¹ Demirel et al.; ⁵³ Ihm et al. ⁵⁷	● (green) ● (yellow) ● (red)	Ergaz et al. ¹⁶ Deindl et al. ⁶¹ Hapnes et al. ⁴⁰
NEC	● (green) ● (red)	Cabannes et al. ⁵¹ Demirel et al. ⁵³		
Asphyxia			● (green) ● (red)	Brotschi et al. ⁵⁰ Gallotti et al. ⁵⁶
Thrombophilia			● (green)	Levit et al. ³⁴
Family history of thrombophilia	● (green)	Cabannes et al. ⁵¹		
Polycythaemia	● (yellow) ● (red)	Narang et al. ⁵⁹ Demirel et al. ⁵³		
Dehydration	● (green) ● (red)	Cabannes et al. ⁵¹ Demirel et al. ⁵³		
Thrombocytopenia	● (yellow)	Narang et al. ⁵⁹		
CHD	● (yellow) ● (red)	Aiyagari et al. ⁴⁸ Demirel et al. ⁵³		
Down syndrome	● (red)	Demirel et al. ⁵³		
Maternal lupus			● (red)	Franco et al. ⁵⁵
TTTS (recipient)			● (yellow)	Deindl et al. ⁶¹
MAS	● (red)	Demirel et al. ⁵³		
RDS	● (red)	Demirel et al. ⁵³	● (yellow)	Deindl et al. ⁶¹
Hyperbilirubinaemia	● (red)	Demirel et al. ⁵³		
Exchange transfusion	● (red)	Demirel et al. ⁵³		
Device				

Table 3 (continued)

Risk factors	UVCs	UACs
Longer dwell time (>5 days)	Levit et al. ³⁴	Levit et al.; ³⁴ Ergaz et al. ¹⁶
	Aiyagari et al.; ⁴⁸ Arnts et al. ⁴⁹	Hapnes et al.; ⁴⁰ Kayiran et al. ⁵⁸
Malposition	Dubbink-Verheji et al., ⁵⁴ Cabannes et al. ⁵¹	
	Abiramalatha et al., ⁴⁷ Ihm et al., ⁵⁷ Poonai et al. ⁶²	
Hepatic extravasation	Chen et al. ⁵²	

UVC: umbilical venous catheter; UAC: umbilical arterial catheter; LBW: low birth weight; NEC: necrotising enterocolitis; SGA: small for gestational age; PE: pre-eclampsia; CHD: congenital heart disease; TTTS: twin-to-twin transfusion syndrome; MAS: meconium aspiration syndrome; RDS: respiratory distress syndrome.

3.2.3. Malposition and migration

The risk factors for UVC and UAC malposition or migration are presented in Table 4. LBW and prematurity were reportedly associated with migration or malposition of the UVC in case studies.^{42,47,62,64,65,67,69,71–77,79–82,84,87–93} Chen et al.⁵² reported similar demographics among neonates with a correct UVC position and those with malposition in this cohort (30.3 ± 3.2 weeks and 1513.1 ± 407.3 grams vs. 30.5 ± 3.3 weeks and 1546.3 ± 412.7 grams, respectively). However, Gupta et al.⁶⁸ found no association in the LBW cohort.

The methods used to estimate insertion length have been demonstrated to be inaccurate in prospective studies,^{54,66} thus being a risk factor for malposition, with 70% malpositioned on ultrasound proceeding insertion.⁶⁶ Similar results were found in a prospective study by Dubbink-Verheij et al.,⁵⁴ demonstrating correct tip location in only 13% of neonates and the tip to be positioned too high in 84% neonates.

Migration of the UVC was most frequently identified in the first 48 h after insertion and noted to decrease over time when surveyed serially in prospective cohort studies citing taping or securement and drying of the umbilical stump as possible aetiologies.^{7,66,68,83} UVC dwell times of longer than 5 days were a feature of case studies reporting serious adverse events associated with catheter migration.^{42,63,69,73,74,77,80–82,89,93} Longer dwell times were reported as risk factors for migration in cohort studies by Franta et al.⁶⁶ and Chen et al.⁵² Congenital abnormalities such as diaphragmatic hernia, intestinal atresia, and heart defects complicated correct umbilical tip placement and resulted in malposition owing to structural abnormalities.^{71,78,90,91,94,97}

No studies reported risk factors for UAC malposition or migration. Accidental dislodgement of the UAC was reported in 4% of patients in a retrospective study by DeWitt et al.⁹⁵ during transportation to the catheterisation laboratory or during insertion itself. In a prospective observational study, regular skin-to-skin contact did not increase risk of dislodgment of the UVC.⁹⁶

3.2.4. Extravasation

Two cohort studies that examined risk factors for UVC-related extravasation were identified (Table 5).^{34,52} Neonates with extravasation were premature and most likely were LBW ($p < 0.0001$). The predisposing factor for extravasation was the presence of malpositioned catheter tips compared with correctly positioned tips ($p < 0.0001$).⁵² In the study by Levit,³⁴ two effusions were associated with malposition of the tip.

The remainder of the studies that reported extravasation described a combination of UVC tip malposition and the infusion of hyperosmolar fluids, resulting in damage to the surrounding hepatic parenchyma or cardiac compromise (Table 5).^{42,63–65,67,69,71–78,80,82,84,87–89,91,93,98–100} In the autopsy

study by Warren et al.,⁹³ four neonates died of sudden unexpected cardiac arrest owing to pericardial effusion and cardiac tamponade, and the authors suspected extravasation of TPN when the UVC tips were located within the RA. However, eight case studies reported neonates who were LBW with TPN extravasation associated with a correctly positioned UVC.^{101–108}

The influence of UVC dwell time of more than 5 days on extravasation incidence was analysed in a retrospective cohort study,⁵² but it was found that it was not statistically significant ($p = 0.262$). Case studies reporting extravasation featured an UVC dwell time of >5 days.^{42,63,69,73,74,77,80,82,84,89,93,106,107} Four case studies reported extravasation associated with a double-lumen UVC,^{65,71,76,100} a silicone catheter,⁹⁹ and a brand of polyurethane UVC.⁷⁴ Anatomical abnormalities such as congenital diaphragmatic hernia and intestinal atresia resulted in catheter malposition and extravasation of hyperosmolar fluids through the UVC.^{71,78,91}

3.2.5. Other adverse events

3.2.5.1. Iatrogenic events associated with insertion. Eight case studies reported vessel, liver, or tissue damage including umbilical pseudoaneurysm with hemoperitoneum or aortic perforation during UAC and UVC insertion in preterm neonates.^{11,12,33,84,110–112} Three reported multiple attempts to successfully insert the catheter in premature newborns^{12,33,112} or catheter manipulation before the iatrogenic event.¹¹¹ A silicone UAC broke after insertion in a premature LBW neonate in the case study by Doğan et al.,¹¹³ requiring retrieval under fluoroscopic guidance.

Incorrect assessment of the umbilical anatomy at the time of insertion was reported in three case studies. A neonate developed glutaeal necrosis when hyperosmolar fluids were accidentally administered into the artery without tip confirmation first.¹¹⁴ Takci et al.¹¹⁵ reported a case of an UVC incorrectly inserted into the umbilical artery with infusion of dextrose for 9 days, resulting in hyperinsulinemia and hypoglycemia. Accidental perforation of the appendix occurred when an appendix had congenitally herniated into the umbilical cord, and the umbilicus was excised.¹¹⁶

3.2.5.2. Necrotising enterocolitis. In a prospective cohort study of 132 preterm neonates,⁸⁶ BW (OR = 2.2, 95% CI = 1.2–4.7, $p = 0.001$) and UVC malposition (OR = 6.9, 95% CI = 1.6–35.4, $p = 0.007$) were independent and significant predictive factors for developing NEC.

4. Discussion

Umbilical catheters provide vital vascular access for neonates; however, they are not without risk. This scoping review is the first to review umbilical catheters in the neonatal population to identify the breadth of potential adverse events and associated risk factors

Table 4

The prevalence of risk factors for catheter malposition or migration and risk of bias in the studies.



CDH: congenital diaphragmatic hernia; CHD: congenital heart disease; LBW: low birth weight; UAC: umbilical arterial catheter.

to inform future research and guide clinicians in safe umbilical catheter management (**Figs. 3 and 4**).

4.1. Umbilical venous catheters

Level I and II evidence report that longer dwell time increases the risk of BSI, thrombosis, and malposition. LBW is also associated with increased risk of BSI, malposition, and extravasation. Tip malposition with the infusion of hyperosmolar fluid can cause extravasation, leading to organ and vessel damage, and when coupled with being LBW, the risk of developing NEC increases. In

addition, maternal diabetes, a history of thrombophilia, and neonatal sepsis can increase risk of thrombosis. The remainder of the risk factors were reported in case studies and are therefore interpreted with a significant degree of caution. However, there was homogeneity in the risk factors identified amongst these case studies that warrant further investigation, particularly in relation to catheter surveillance as dwell time increases.

4.1.1. BSIs associated with UVCs

Eight large cohort studies included in this review demonstrated an association between increased dwell time of UVCs and the

Table 5

Risk factors for extravasation associated with umbilical catheter use and risk of bias in the studies.

Risk factors	UVCs
Patient	
LBW	Chen et al. ⁵²
Prematurity	Warren et al.; ⁹³ Oztan; ⁷⁵ Elbatreen et al.; ¹⁰⁴ Guzoglu et al.; ¹⁰⁵ Hagerott et al.; ⁶⁹ Ozdemir et al.; ¹⁰⁸ Pegu and Murthy; ⁷⁶ Kumar and Murki; ¹⁰⁶ Unal et al.; ¹⁰⁹ Egyepong et al.; ⁶⁵ Mahajan et al.; ⁷⁴ Montaruli et al.; ¹⁰⁷ Abiramalatha et al.; ⁸⁷ Gülcen et al.; ⁶⁷ Khaladkar et al.; ⁷³ Grizelj; ⁷⁷ Sharma et al.; ⁴² Garg et al.; ¹⁰⁹ Chioukh et al.; ¹⁰³ Turk et al. ⁹¹
RDS	Chen et al. ⁵²
CDH	Warren et al.; ⁹³ Hartley et al.; ⁷² Oztan; ⁷⁵ Hargitai et al.; ⁷¹ Ahmed et al.; ¹⁰¹ Elbatreen et al.; ¹⁰⁴ Guzoglu et al.; ¹⁰⁴ Hagerott et al.; ⁶⁹ Ozdemir et al.; ¹⁰⁸ Bothur-Nowacka et al.; ⁸⁹ Pegu and Murthy; ⁷⁶ Unal et al.; ¹⁰⁹ Egyepong et al.; ⁶⁵ Mahajan et al.; ⁷⁴ Kumar and Murki; ¹⁰⁶ Sherwani et al.; ⁸⁰ Montaruli et al.; ¹⁰⁷ Yeh et al.; ⁸² Abiramalatha et al.; ⁸⁷ Bayhan et al.; ⁶⁴ Gülcen et al.; ⁶⁷ Khaladkar et al.; ⁷³ Grizelj; ⁷⁷ Sharma et al.; ⁴² Fuchs et al.; ⁸⁴ Chioukh et al.; ¹⁰³ Turk et al.; ⁹¹ Alfaro-Cruz et al. ⁸⁸
Intestinal atresia	Turk et al. ⁹¹
Device	
Longer dwell time >5 days	Chen et al. ⁵²
Malposition	Hagerott et al.; ⁶⁹ Ozdemir et al.; ¹⁰⁸ Sherwani et al.; ⁸⁰ Yeh et al.; ⁸² Montaruli et al.; ¹⁰⁷ Khaladkar et al.; ⁷³ Sharma et al.; ⁴² Adesanya and Naqvi; ⁶³ Bothur-Nowacka et al.; ⁸⁹ Grizelj; ⁷⁷ Fuchs et al.; ⁸⁴ Mahajan et al.; ⁷⁴ Warren et al. ⁹³
Hyperosmolar fluid (no malposition)	Elbatreen et al.; ¹⁰⁴ Ahmed et al.; ¹⁰² Guzoglu et al.; ¹⁰⁵ Ozdemir et al.; ¹⁰⁸ Unal et al.; ¹⁰⁹ Kumar and Murki; ¹⁰⁶ Montaruli et al.; ¹⁰⁷ Chioukh et al. ¹⁰³
Malposition + hyperosmolar fluid	Levit et al. ³⁴
Double-lumen catheter	Warren et al.; ⁹³ Saboo et al.; ¹⁰¹ Hartley et al.; ⁷² Oztan; ⁷⁵ Türk et al.; ⁹¹ Hagerott et al.; ⁶⁹ Bothur-Nowacka et al.; ⁸⁹ Pegu and Murthy; ⁷⁶ Adesanya and Naqvi; ⁶³ Sherwani et al.; ⁸⁰ Mahajan et al.; ⁷⁴ Yeh et al.; ⁸² Bayhan et al.; ⁶⁴ Gülcen et al.; ⁶⁷ Grizelj; ⁷⁷ Sharma et al.; ⁴² Abdellatif et al.; ⁹⁸ Fuchs et al.; ⁸⁴ Abiramalatha et al.; ⁸⁷ Khaladkar et al.; ⁷³ Hargitai et al.; ⁷¹ Raisanen et al.; ⁷⁸ Megha et al.; ¹⁰⁰ Alfaro-Cruz et al.; ⁸⁸ Egyepong et al. ⁶⁵
Brand (+polyurethane)	Saboo et al.; ¹⁰¹ Egyepong et al.; ⁶⁵ Hargitai et al.; ⁷¹ Pegu and Murthy ⁷⁶
Silicone catheter	Mahajan et al. ⁷⁴
Provider	
Multiple attempts at insertion	Megha et al. ⁹⁹
Egyepong et al.; ⁶⁵ Saboo et al.; ¹⁰¹ Fuchs et al.; ⁸⁴ Mahajan et al. ⁷⁴	

CDH: congenital diaphragmatic hernia; UVC: umbilical venous catheter; LBW: low birth weight; RDS: respiratory distress syndrome.

development of BSIs, recommending early removal.^{31,32,34,36–39,43} There has only been one RCT identified in a Cochrane review investigating the effect of planned early removal of UVCs with replacement of a peripherally inserted central catheter (PICC) in premature neonates.¹¹⁷ In this study, there was no difference in the incidence of catheter-related BSI, hospital mortality or morbidity between early and prolonged use of UVCs. This single RCT is insufficient to demonstrate the efficacy of early removal, and further research is required to make definitive conclusions. In addition, the present review identified only one study investigating the effect of an antibiotic-coated UVC that resulted in a significant reduction in BSI. Further research needs to be conducted to determine if the use of an antibiotic-impregnated catheter may mitigate the need for early UVC removal.

4.1.2. Thrombosis

Maternal illness such as diabetes, pre-eclampsia, and a family history of thrombophilia were reported as associations for UVC-associated thrombosis.^{51,59} Neonatal sepsis, polycythaemia, respiratory distress syndrome, meconium aspiration syndrome,

hyperbilirubinaemia, dehydration, and congenital heart defects were also described as patient risk factors.^{16,31,48,49,53,54} Further investigation into the potential causal relationships with these illnesses is required in conjunction with screening methods to detect thrombi in these populations.

Longer duration of UVC placement (>5 days) was associated with catheter thrombosis in three large cohort studies.^{34,48,49} Moreover, infusion of low-dose heparin appears to not change the incidence of UVC-associated thrombi.⁶⁰ Prospective studies have demonstrated the benefit of ultrasound in detecting asymptomatic thrombi to reduce progression to local and systemic symptoms.^{16,51} Thus, the use of serial ultrasound may be an essential component of care in neonates who require UVCs for longer duration rather than replacement of a PICC.

4.1.3. Mechanical events

More than 50% of the studies included in this review were case studies detailing major and, on some occasions, fatal adverse events as a direct result of UVC malposition such as NEC, extravasation, and pericardial or pleural effusion. Many reported the infusion of

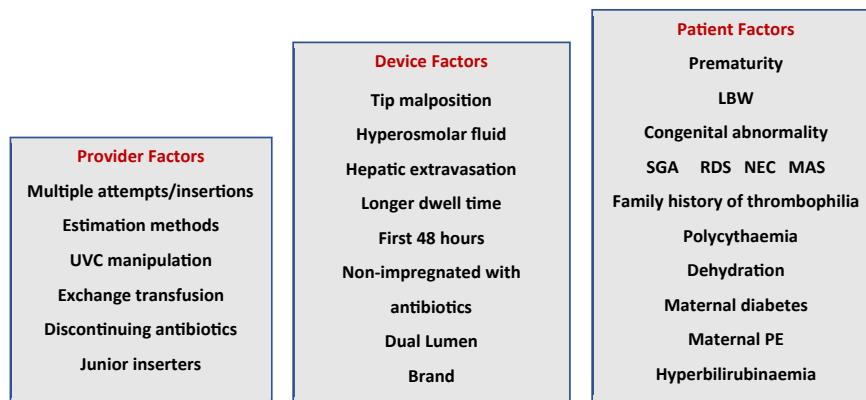


Fig. 3. A visual representation of the potential risk factors associated with UVCs. LBW: low birth weight; SGA: small for gestational age; RDS: respiratory distress syndrome; NEC: necrotising enterocolitis; MAS: meconium aspiration syndrome; PE: pre-eclampsia; UVC: umbilical venous catheter.

hyperosmolar fluids through a malpositioned UVC that resulted in liver damage. The inaccuracy of insertion length estimation methods for the premature population resulting in malposition has been demonstrated.^{66,118–120} Researchers detected that most catheters which were confirmed to be in an appropriate location by standard X-ray imaging were inappropriately placed using ultrasound. These studies suggest ultrasonography may be superior to X-ray imaging to determine the true location of the catheter tip in preterm populations. The use of bedside ultrasound when inserting umbilical catheters and confirming the tip location may facilitate successful insertion and alleviate the need for radiography, reducing radiation exposure.¹²¹

It has been demonstrated that nearly all UVCs migrate over time from their original correct position during the first 48 h as the umbilical stumps dries, causing the catheter to migrate inwards.⁷ The influence of factors associated with catheter movement such as taping and securement⁷ and abdominal girth changes^{66,122,123} requires further investigation to manage internal and external movement. In addition, the development of novel catheter technology to prevent catheter migration is necessary.

In a survey of 187 American NICUs, all obtained a radiograph immediately after central line placement, but only 18% obtained a routine radiograph 24 h after line insertion. Only 45% of NICUs obtained subsequent radiographs to evaluate tip location, and fewer had a standard protocol.¹²⁴ As nearly all UVCs migrate, serial surveillance measures need to be implemented to ensure the correct location of the catheter tip is maintained, particularly during the infusion of high osmolarity fluids. Currently, there are no clinical practice standards to guide clinicians to the frequency and method used to monitor tip location.

4.2. Umbilical arterial catheters

Overall, there was a lack of level I and II evidence investigating risk factors for adverse events associated with UACs, with research focussing primarily on UVC- or UAC-associated thrombosis.

4.2.1. BSIs associated with UACs

We only identified one cohort study that reported risk factors for BSI associated with UACs. This is an alarming finding as UAC-associated BSI incidence has been reported as 4.4 per 1000 catheter days versus 3.8 per 1000 catheter days for UVCs.¹²⁵ Arterial catheters may be an under-recognised cause of catheter-related BSI¹²⁶, and the incidence of colonisation, major infection, and BSI is not different between arterial catheters and CVCs.¹²⁷ This highlights the need for further research into the predictors of UAC-associated BSI.

4.2.2. Thrombosis

This scoping review identified only four cohort studies investigating risk factors for thrombosis. Longer duration of UAC (>5 days) was associated with catheter thrombosis in four large cohort studies.^{16,34,50,61} Moreover, infusion of low-dose heparin appears to not reduce the incidence of UAC-related thrombi.^{16,128} Patient characteristics increase the risk including LBW, prematurity, neonatal sepsis, birth asphyxia, thrombophilia, twin-to-twin transfusion syndrome, respiratory distress syndrome, and maternal lupus. Peripheral arterial catheters are also prone to malfunction and adverse events such as limb ischemia.¹²⁹ The benefit of planned early removal of UACs with replacement of a peripheral arterial

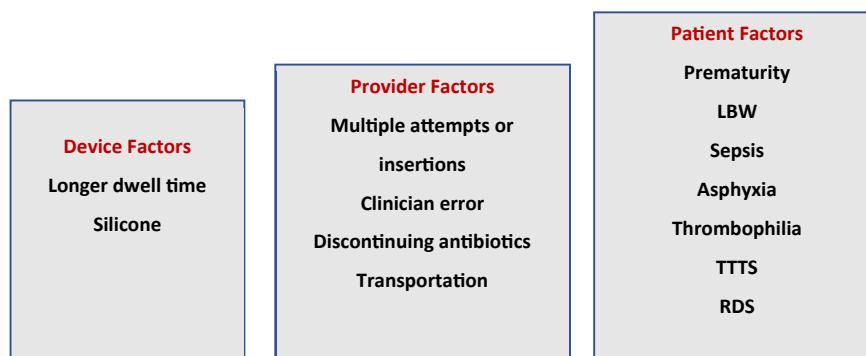


Fig. 4. A visual representation of the potential risk factors associated with UACs. LBW: low birth weight; TTTS: twin-to-twin transfusion syndrome; RDS: respiratory distress syndrome; UAC: umbilical arterial catheter.

catheter for continuous arterial access has not been studied and is a research priority in this field.

The remainder of the studies investigating risk factors for UAC-associated adverse events were case studies detailing adverse events during insertion. In two of the included studies in this review, insertion was complicated by difficulty with backflow of blood or resistance of the catheter to thread, which resulted in aortic perforation.^{5,112} As for UVCs, the use of ultrasound for easier insertion and tip surveillance to prevent damage to the artery may be warranted, and this requires further investigation.

5. Limitations

This scoping review is a broad overview of published works of the possible risk factors for adverse events associated with umbilical vascular catheters occurring during and after insertion. The heterogeneity in study methodology and predominance of case studies in this review makes direct comparisons of the results difficult and statistical analysis unfeasible. This scoping review is limited in that it did not thoroughly evaluate the quality of evidence and did not include publications in other languages; therefore, the results should be interpreted with caution.

6. Conclusion

This scoping review identified a diverse range of potential risk factors for adverse events associated with umbilical catheter use, including patient, device, and provider factors. More than half of the research studies examining risk factors for umbilical vascular adverse events are case studies reporting a serious adverse event, most commonly, catheter migration. The remainder are predominantly retrospective cohort studies that report conflicting research outcomes. This scoping review has identified a variety of possible risk factors that may inform a large cohort study or RCT design to rigorously evaluate the association between risk factors and adverse events. Regular catheter surveillance will provide inter-hospital benchmarking and may reduce adverse events such as catheter malposition, migration, and extravasation of hyperosmolar fluids.

Conflict of Interest

The authors have no competing interests to declare. Independent from the reported project, Griffith University has received investigator-initiated research and educational grants from product manufacturers (3M, Becton Dickinson, Cardinal Health), to support research led by AU (her former employer). Independent from this project, Griffith University has received investigator-initiated research and educational grants from product manufacturers (3M, Access Scientific, BD/Bard, Medical Specialties Australasia, Vygon), to support research led by T.K. Smiths Medical Australia to T.K.

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Author contribution

All authors have approved the final article, have made substantial contributions to the review, are accountable for the work presented, and acknowledge that they are entitled to authorship of this article.

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