Guideline



# Clinical practice guidelines for the management of central venous catheter for critically ill patients

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**Abstract:** The objective of this article is to provide a guideline for the management of central venous catheter for critically ill patients. Electronic databases of CENTRAL, CINAHL, EMBASE, four Chinese databases (CBM, WANFANG DATA, CAJD, VIP Database) and Google Scholar were searched from inception to August 2017. The reviewers assessed each included study for the risk of bias under the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. The GRADE evidence profile tables were added to each important clinical outcome. The guideline will be updated in a 5-year interval by incorporating new evidence. The guideline panel provided 11 statements on the management of central venous catheter for critically ill patients. Overall, there were 4 strong recommendations, and 7 weak recommendations. They were as follows: (I) we commend the use of catheter impregnation to prevent catheter-related blood stream infection (1A); (II) we suggest the use of real-time ultrasound guidance for subclavian or femoral vein insertion (2B), and recommend that for internal jugular vein (1A); (III) we suggest the use of real-time color Doppler ultrasound guidance on central venous catheterization for adult and pediatric patients (2C); (IV) we suggest not to use heparin for the maintenance of CVC patency (2A); (V) we suggest the use contrast-enhanced ultrasound for the confirmation of central venous catheter placement (2B); (VI) we recommend the use of bedside ultrasound together with agitated or non-agitated normal saline to confirm CVC position (1C); (VII) we suggest to use subclavian site for CVC insertion (2C); (VIII) we suggest not to use heparin-bonded catheters or warfarin to prevent CVC-related deep vein thrombosis in children (2D); (IX) we recommend the implementation of central-line bundles to reduce the risk of CRBSI for adult, pediatric and neonatal ICUs (1B); (X) we suggest skin antisepsis with chlorhexidine throughout in-dwelling period for reducing CVC-related infections (2D); (XI) we recommend a differential time to positivity (DTP) of blood cultures from CVC and peripheral vein of 120 minutes to diagnose CRBSI (1B). Substantial agreement exists among experts for issuing strong recommendations for the management of central venous catheter. Although a significant number of aspects of care have relatively weak support, evidence-based recommendations regarding the management of central venous catheter are the foundation of improved outcomes for critically ill patients.

**Keywords:** Central venous catheter; clinical practice guideline; critically ill; critical care; ultrasound

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## Introduction

Central venous catheter (CVC) is one of the most commonly used interventions in the critically ill patients. Reasons for inserting a CVC include rapid administration of fluids during resuscitation periods, monitoring of hemodynamic status, administration of vasoconstrictors or veno-sclerotic drugs and, using large bore catheters, for the purposes of hemofiltration. Also, some drugs or fluids such as parental nutrition, potassium solution, strong vasoconstrictors and chemotherapy drugs must be given via CVC. However, CVC is an invasive technique and should be managed properly to minimize potential risks. Some catastrophic complications of CVC placement include pneumothorax, artery injury, blood stream infection, thrombosis, and human errors such as air embolism and unintentional guidewire embolization. Clinicians should weigh the risks and benefits before deciding to insert CVCs. However, such a widely used treatment tool lacks formal guidelines and the clinical practice patterns are heterogeneous. The Asian society of emergency and critical care medicine convened a consensus meeting and drafted a clinical practice guideline for the management of CVC. The guideline was developed under the framework of The Appraisal of Guidelines for Research & Evaluation II instrument (AGREE II).

### *Scope and purpose*

The guideline aims to provide evidence based state-of-the-art guidelines for the management of CVC in the intensive care unit in all critically ill patients treated in the ICU. The guideline covers topics of indications and contraindications of CVC insertion, strategies to lower complications related to the CVC insertion, maintenance of CVC and prevention of CVC-related complications (e.g., thrombosis, blood stream infection). The purpose is to increase the benefits of CVC, while keeping risks at the lowest level. The views and preferences of the patients in ICUs were sought by literature review. If an intervention or treatment was unacceptable for patients or their family members, the recommendation of the intervention or treatment would be downgraded.

### *Stakeholder involvement*

The guideline development group included intensivist, critical care nurses, personnel from infection control department and emergency physicians. The target users of the guideline included intensivist, critical care nurses, emergency physicians and policymakers. The guideline aimed to inform clinical decision making such as when to insert a CVC, should ultrasound be a routine for guiding CVC placement and what solution can be used to keep catheter patency. Also the guideline can be used for policy making such as nursing bundle for the prevention of catheter-related blood stream infection (CRBSI).

### *Development of recommendations*

Electronic databases of CENTRAL, CINAHL, EMBASE, four Chinese databases (CBM, WANFANG DATA, CAJD, VIP Database) and Google Scholar were searched from inception to August 2017. The core search terms included "central venous catheter" and "critical care". All relevant items were screened and reviewed.

The inclusion criteria were (I) clinical studies conducted in ICU; (II) the study investigated clinical questions related to the CVC; (III) systematic review and meta-analysis had the priority to be included. Studies were excluded if (I) they were duplicated report of the same work; (II) a meta-analysis that had been updated by a new one with more recent publications; (III) articles rather than original articles such as letters, reviews and commentaries. Review articles were reviewed manually to identify additional original studies. If there were no updated systematic review and meta-analysis, we would perform it by adding new studies.

The strengths and limitations of the body of evidence underlying a recommendation were clearly described. The risk of bias for included clinical studies were assessed from the aspects of study design, methodology limitations (sampling, blinding, allocation concealment, analytical methods), appropriateness/relevance of primary and secondary outcomes considered, consistency of results across studies, direction of results across studies, magnitude of benefit versus magnitude of harm, applicability to practice context (1,2).

The reviewers assessed each included study for the risk of bias under the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework (1,2). State-of-the-art instruments of quality assessment were used: Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 for studies of diagnostic accuracy (3,4), Cochrane for randomized controlled trials (RCTs) (5), and GRADE for observational studies that inform both therapy and prognosis questions. The GRADE

 

**Table 1** Level of evidence and strength of recommendation

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|---|
| Strength of recommendation |
| Strong recommendation is the one that deemed appropriate by the large majority of experts with no major dissension. The desirable effects of adherence to the recommendation outweigh the undesirable effects. We use the word "recommend" or "recommend not to" for strong recommendation |
| Weak recommendation is the one deemed appropriate by the majority of experts, but some degree of dissension exists. The desirable effects of adherence to the recommendation probably outweigh the undesirable effects. We use the word "suggest" or "suggest not to" for strong recommendation |
| Level of evidence |
| Grade A: high level of evidence (⊕⊕⊕⊕). The true effect is close to our estimate of the effect |
| Grade B: moderate level of evidence (⊕⊕⊕◯). The true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different |
| Grade C: low level of evidence (⊕⊕◯◯). The true effect may be substantially different from our estimate of the effect |
| Grade D: very low level of evidence (⊕◯◯◯). Our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect |

evidence profile tables were added to each important clinical outcome. These important outcomes were risk of blood stream infection, lumen patency, thrombosis, artery injury and pneumothorax. The follow-up time was the period of the in-hospital stay. Based on the study methodologies and the 5 core GRADE domains of risk of bias, inconsistency, indirectness, imprecision, and other considerations (including publication bias), the quality of the evidence (or confidence in the estimate of the effect) was categorized as high, moderate, low, or very low. Recommendations were then formulated by using the modified Dephi method. These recommendations were designated as either strong or weak, taking into account an overall assessment of the evidence and a statement from the task force about the values and preferences that underlie the recommendations. We use the word "recommend" to indicate a strong recommendation and "suggest" to indicate a weak recommendation (*Table 1*).

The guideline will be updated in a 5-year interval by incorporating new evidence.

## Results

### *We commend the use of catheter impregnation to prevent CRBSI (1A)*

There is a Cochrane review updated in the year 2016 and this review provided state-of-the-art evidence for making recommendations (6). In the systematic review, a total of 57 studies were included into analysis, the summary results are shown in *Table 2*. Many study end points including CRBSI, catheter colonization, clinically diagnosed sepsis and all cause-mortality were evaluated. Most studies (42/57) reported CRBSI as the primary end-point. The quality of included RCTs was considered to be high because there was no impairment of the five domains. The result showed that catheter impregnation significantly reduced CRBSI as compared with non-impregnated catheters with a relative risk of 0.62 (95% CI: 0.52–0.74). The number needed to treat to benefit (NNTB) is 50. Because CRBSI is an important indicator of the quality of nosocomial infection control, we considered it as an important outcome. In contrast, the catheter colonization was considered as a less important outcome. The result showed that the impregnated catheters were able to reduce the risk of catheter colonization (RR 0.67; 95% CI: 0.59–0.76). A total of 12 studies reported the incidence of clinically diagnosed sepsis, but impregnated catheters were not able to reduce the risk (RR 1.00; 95% CI: 0.88–1.13). All-cause mortality was the most important outcome for the ICU patients, and a total of 10 studies reported this end-point. Although there was a marginal benefit of the impregnated catheter (RR 0.92; 95% CI: 0.80–1.07), statistical significance was not reached (*Table 2*).

However, the medical cost associated with the impregnated catheter was not reported in the Cochrane systematic review. Numerous studies have reported that the use of impregnated catheter could reduce CVC-related costs (7). The chlorhexidine-silver sulfadiazine (CHSS)-impregnated catheters were associated with lower CVC-

 

**Table 2** Evidence profiles for the question of Antimicrobial CVC versus comparators in unselected critically ill patients

| No. of studies | Quality assessment | | | | | | No. of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Antimicrobial CVC | Comparator | Relative (95% CI) | Absolute (95% CI) | | |
| CRBSI | | | | | | | | | | | | |
| 42 | RCT | Low 1 | Not serious | Not serious | Not serious | None | 177/5,215 | 294/5,190 | RR 0.62 (0.52–0.74) | NNTB: 50 | ⊕⊕⊕⊕ High | Critical |
| Catheter colonization | | | | | | | | | | | | |
| 43 | RCT | Low 1 | Serious | Not serious | Not serious | None | 935/5,040 | 1,320/4,870 | RR 0.67 (0.59–0.76) | NNTB: 11 | ⊕⊕⊕◯ Moderate | Moderate |
| Clinically diagnosed sepsis | | | | | | | | | | | | |
| 12 | RCT | Low 1 | Not serious | Not serious | Not serious | Publication bias | 320/1,845 | 317/1,841 | RR 1.00 (0.88–1.13) | | ⊕⊕⊕◯ Moderate | Critical |
| All-cause mortality | | | | | | | | | | | | |
| 10 | RCT | Low 1 | Not serious | Not serious | Not serious | None | 252/1,319 | 268/1,324 | RR 0.92 (0.80–1.07) | | ⊕⊕⊕⊕ High | Critical |

Overall, there were low or unclear risks of bias for most criteria, except blinding. The majority of included studies (n=47) had an unclear or high risk of bias for blinding of participants and personnel. In contrast, more than half of included studies (n=34) had a low risk of bias in selective reporting. CI, confidence interval; RR, risk ratio; NNTB, number need to treat to benefit; CVC, central venous catheter; CRBSI, catheter-related blood stream infection; RCT, randomized controlled trial.

related cost per day than standard catheters (€3.78 ± €4.45 *vs.* €7.28 ± €16.71, respectively) (8). The cost-effectiveness study of impregnated versus non-impregnated CVC were reported in an earlier systematic review. The economic performance of impregnated catheter was analyzed using a basic decision-analytic model and the results showed that there is an estimated cost-saving of 138.20 pounds for every patient who receives an impregnated CVC (9). Based on these evidence, we recommend the impregnated CVC for critically ill patients.

### *We suggest the use of real-time ultrasound guidance for subclavian or femoral vein insertion (2B), and recommend that for internal jugular vein (1A)*

Common complications of CVC insertion included artery injury, pneumothorax, repeated attempts, hematoma and hemorrhage. Numerous efforts have been made in clinical investigations to minimize the risk associated with CVC insertion. The real-time ultrasound guidance was employed in many studies to improve the success rate and reduce complications.

A systematic review deposited in the Cochrane database included 13 studies investigating the use of US-guided subclavian or femoral vein insertion in adult population (10). The quality of evidence was low in 4 studies (11-14) involving subclavian and 1 studies (15) involving femoral vein, very low in three studies (16-18) involving subclavian vein (SV) for most outcomes, moderate for 1 study involving femoral vein and high for 1 study (19) involving SV. Overall, the quality of evidence was low and the US-guidance offers small gains in safety and quality when compared with an anatomical landmark technique for femoral vein (success on the first attempt) cannulation or subclavian (arterial puncture, haematoma formation) (*Tables 3*,*4*). For internal jugular vein (20), there was evidence that the use of two dimensional (2D) US-guidance reduced the number of participants with an inadvertent arterial puncture by 72% (4,388 participants in 22 studies, RR 0.28, 95% CI: 0.18 to 0.44; P value <0.00001, $I^2$ =35%), and the risk of overall complications by 71% (2,406 participants in 14 studies, RR 0.29, 95% CI: 0.17 to 0.52; P<0.0001, $I^2$ =57%). Overall success rates were modestly increased in overall groups at 12% (4,340 participants in 23 studies, RR 1.12, 95% CI: 1.08 to 1.17; P value <0.01, $I^2$ =85%), and similar benefit was noted across all subgroups. Use of 2DUS increased the success rate at the first attempt by 57% (2,681 patients in 18 studies, RR 1.57, 95% CI: 1.36

 

**Table 3** Real-time ultrasound guidance compared to landmark procedure for internal jugular vein catheterization

| No. of studies | Quality assessment | | | | | | No. of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Real-time ultrasound guidance | Landmark procedure | Relative (95% CI) | Absolute (95% CI) | | |
| Total complications (follow up: mean 10 days) | | | | | | | | | | | | |
| 6 | Randomised trials | Not serious | Not serious | Not serious | Not serious | None | 53/733 (7.2%) | 83/745 (11.1%) | RR 0.52 (0.23 to 1.17) | 53 Fewer per 1,000 (from 19 more to 86 fewer) | ⊕⊕⊕⊕ High | Critical |
| Overall success rate | | | | | | | | | | | | |
| 8 | Randomised trials | Not serious | Not serious | Not serious | Not serious | None | 818/897 (91.2%) | 800/912 (87.7%) | RR 1.05 (0.97 to 1.13) | 44 more per 1,000 (from 26 fewer to 114 more) | ⊕⊕⊕⊕ High | Critical |
| Number of attempts until success | | | | | | | | | | | | |
| 15 | Randomised trials | Not serious | Not serious | Not serious | Not serious | None | 1,650 | 1,652 | – | MD 1.19 times lower (1.45 lower to 0.92 lower) | ⊕⊕⊕⊕ High | Important |
| Arterial puncture | | | | | | | | | | | | |
| 22 | Randomised trials | Not serious | Not serious | Not serious | Not serious | Strong association | 44/2,196 (2.0%) | 205/2,192 (9.4%) | RR 0.28 (0.18 to 0.44) | 67 Fewer per 1,000 (from 52 fewer to 77 fewer) | ⊕⊕⊕⊕ High | Critical |
| Haematoma formation | | | | | | | | | | | | |
| 13 | Randomised trials | Not serious | Serious[a] | Not serious | Not serious | Strong association | 26/1,629 (1.6%) | 108/1,604 (6.7%) | RR 0.27 (0.13 to 0.55) | 49 Fewer per 1,000 (from 30 fewer to 59 fewer) | ⊕⊕⊕⊕ High | Critical |
| Other complications (thrombosis, embolism, haematomediastinum and hydromediastinum, haematothorax and hydrothorax, pneumothorax, subcutaneous emphysema, nerve injury) | | | | | | | | | | | | |
| 11 | Randomised trials | Not serious | Not serious | Not serious | Not serious | None | 9/1,528 (0.6%) | 45/1,514 (3.0%) | RR 0.34 (0.15 to 0.76) | 20 Fewer per 1,000 (from 7 fewer to 25 fewer) | ⊕⊕⊕⊕ High | Critical |
| Time to successful cannulation | | | | | | | | | | | | |
| 19 | Randomised trials | Not serious | Serious[b] | Not serious | Serious[c] | None | 1,718 | 1,733 | – | MD 30.52 sec lower (55.21 lower to 5.82 lower) | ⊕⊕◯◯ Low | Important |
| Success with attempt number 1 | | | | | | | | | | | | |
| 18 | Randomised trials | Not serious | Serious[d] | Not serious | Not serious | None | 1,085/1,362 (79.7%) | 661/1,319 (50.1%) | RR 1.57 (1.36 to 1.82) | 286 more per 1,000 (from 180 more to 411 more) | ⊕⊕⊕◯ Moderate | Important |
| Success with attempt number 2 | | | | | | | | | | | | |
| 6 | Randomised trials | Not serious | Serious[d] | Not serious | Not serious | None | 553/578 (95.7%) | 482/578 (83.4%) | RR 1.19 (1.07 to 1.32) | 158 more per 1,000 (from 58 more to 267 more) | ⊕⊕⊕◯ Moderate | Not important |
| Success with attempt number 3 | | | | | | | | | | | | |
| 2 | Randomised trials | Not serious | Serious[d] | Not serious | Serious[e] | None | 90/92 (97.8%) | 88/97 (90.7%) | RR 1.22 (0.66 to 2.28) | 200 more per 1,000 (from 308 fewer to 1,000 more) | ⊕⊕◯◯ Low | Not important |

[a], There is heterogeneity observed with an $I^2$ =0.54 (P=0.01), and subgroup analysis failed to explain the heterogeneity; [b], there is heterogeneity ($I^2$ =97%, P<0.001), and subgroup analysis failed to account for the heterogeneity; [c], the lower limit of 95% CI overlapped 10 min, which is a threshold for clinical relevance; [d], there is significant heterogeneity ($I^2$ >50%; P<0.05); [e], the 95% CI: overlaps no effect. CI, confidence interval; RR, risk ratio; MD, mean difference.

**Table 4** Summary of judgements for the ultrasound guidance jugular vein catheterization

| Aspects | Judgement | | | | | | | Implications |
|---|---|---|---|---|---|---|---|---|
| Problem | No | Probably no | Probably yes | Yes | – | Varies | Don't know | |
| Desirable effects | Trivial | Small | Moderate | Large | – | Varies | Don't know | |
| Undesirable effects | Large | Moderate | Small | Trivial | – | Varies | Don't know | |
| Certainty of evidence | Very low | Low | Moderate | High | – | – | No included studies | |
| Values | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | No important uncertainty or variability | – | – | – | |
| Balance of effects | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know | |
| Resources required | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know | |
| Certainty of evidence of required resources | Very low | Low | Moderate | High | – | – | No included studies | |
| Cost effectiveness | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | No included studies | |
| Equity | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know | |
| Acceptability | No | Probably no | Probably yes | Yes | – | Varies | Don't know | |
| Feasibility | No | Probably no | Probably yes | Yes | – | Varies | Don't know | |

to 1.82; P value <0.01, $I^2$ =82%). The number of attempts was decreased in the overall population [3,302 participants in 16 studies, mean difference (MD) −1.19 attempts, 95% CI: −1.45 to −0.92; P value <0.00001, $I^2$ =96%] and in all subgroups. The risk of haematoma formation was reduced by the use of 2DUS-guidance (overall reduction 73%, 3,233 participants in 13 studies, RR 0.27, 95% CI: 0.13 to 0.55; P value =0.0004, $I^2$ =54%). The time to successful CVC insertion was decreased by 30.52 seconds in the 2DUS-guidance group (MD −30.52 seconds, 95% CI: −55.21 to −5.82; P value =0.02, $I^2$ =97%).

Although most of the randomised clinical trials carried out in this area have focused on the internal jugular vein and—to a lesser extent—on the SV it is clear that with growing clinical experience the benefits of ultrasound-guided venipuncture can be extended to all venous access sites, and this is especially true for SV (21). Yet, in a recent RCT a landmark control group was not included in the study because not using US in all patients was considered unethical (21). Moreover, in this study the US-guided infra-clavicular short-axis approach shows some clinical advantages, namely, a higher success rate, less complications and shorter insertion time than long-axis approach. The SV offers multiple advantages as a target for central venous access in the appropriately selected patient. The use of real-time US guidance for infraclavicular placement of SCV catheters allows for direct visualization of needle insertion and adjacent anatomical structures, as well as guidewire location and directionality, all of which can lead to decrease mechanical complications and improve cannulation success, compared to a landmark technique. In our opinion the current literature supports the use of the infraclavicular out-of-plane US-guided SCV catheterization as the preferred technique for cannulation

 

of SV when compared to landmark approach and a solid alternative to cannulation of IJVs.

US usefulness in particular conditions such as obesity should also be considered. Obesity has been described as a risk factor for unsuccessful central venous cannulation or complications; thus, a technique more reliable than one based on anatomic landmarks only is recommended (22). The main findings of the present study are that (1) the anatomic variability of IJV was frequent in morbidly obese patients and (2) a diameter of IJV<10 mm was predictive of difficult positioning, whereas a diameter of IJV <6 mm was predictive of unsuccessful positioning, thus requiring an alternative access.

### *We suggest the use of real-time color Doppler ultrasound (CDUS) guidance on central venous catheterization for adult and pediatric patients (2C)*

The usefulness of CDUS was investigated separately in the Brass's systematic review (20). The chance of success at the first attempt was increased by 58% in the CDUS group (199 participants in 4 studies, RR 1.58, 95% CI: 1.02 to 2.43; P=0.04, $I^2$ =57%). The total numbers of perioperative and postoperative complications/adverse events were similar (93 patients in 3 studies, RR 0.52, 95% CI: 0.16 to 1.71; P=0.28). The overall success rate (289 patients in 7 studies, RR 1.09, 95% CI: 0.95 to 1.25; P=0.20). Other outcomes such as the overall number of participants with an arterial puncture (213 participants in 6 studies, RR 0.61, 95% CI: 0.21 to 1.73; P=0.35), the total number of attempts until success (69 patients in 2 studies, MD –0.63, 95% CI: –1.92 to 0.66; P=0.34) and time to successful cannulation (five trials, 214 patients in 5 studies, each using a different definition for this outcome; MD 62.04 seconds, 95% CI: –13.47 to 137.55; P=0.11) were comparable in the Doppler ultrasound group versus landmark group (*Table 5*).

In pediatric patients (*Table 6*), a recent systematic review involving 8 RCTs were identified (23). The study involved 760 children and infants. The Jadad score was employed for the assessment of the risk of bias (24). One study (25) was scored 2 points, six studies (26-31) were scored 3 points and only one study (32) was scored 4. The forest plot (*Figure 1*) showed that real-time ultrasound guided CVC insertion was able to reduce the risk of CVC insertion failure (RR 0.19; 95% CI: 0.06–0.60). However, the quality of evidence was downgraded due to imprecision and potential publication bias (funnel plot) (33,34). US-guided CVC insertion could also help to decrease the mean number of attempts required (5 studies; difference in number –1.26; 95% CI: –1.711 to –0.812; P<0.001) and the risk of accidental arterial puncture (8 studies; RR 0.359; 95% CI: 0.118–1.093; P=0.071). However, US-guided CVC insertion was not associated with a significant difference in time required for CVC placement (4 studies; difference in minutes: –1.123, 95% CI: –2.600 to 0.353; P=0.136). In conclusion, the US-guided CVC insertion is able to increase the success rate, decrease the number of attempts and the arterial puncture, but will not increase the time for CVC placement. Although the evidence is low, we considered the accidental arterial puncture was an important outcome and there was no significant risk associated with the US, and we strongly recommend using US-guided CVC insertion.

### *We suggest not to use heparin for the maintenance of CVC patency (2A)*

The patency of CVC is of vital importance for its functionality. Thus, strenuous efforts have been made to keep the CVC patency in critically ill patients. We identified several systematic reviews of RCTs comparing heparin and saline in maintaining CVC patency (35,36). We choose the most updated one to make the recommendation (35). The primary purpose of the use of heparin or normal saline was to maintain CVC patency, thus the catheter occlusion was used as the primary end point in the majority of studies. However, catheter occlusion was not patient-important outcome, and the clinical importance was considered as moderate. There were 12 studies reporting this end point and the quality of the evidence was considered as high. Overall, heparin was not able to reduce the risk of catheter occlusion as compared with normal saline (RR 1.21; 95% CI: 0.91–1.61). Two studies reported the Maneuver needed and the results were comparable between the two groups (RR 1.24; 95% CI: 0.71–2.16). The quality of the studies was downgraded because of the confidence interval was wide. The incidence of heparin-induced thrombocytopenia was comparable between heparin and normal saline groups (RR 1.33; 95% CI: 0.09–18.54). The quality was low because there was potential publication bias and wide confidence interval. Three studies reported the incidence of hemorrhage and there was no statistical difference between the two groups. In conclusion, we do not suggest routine use of heparin for CVC patency (*Table 7*).

 

**Table 5** Doppler guidance compared to anatomical landmarks for internal jugular vein catheterization

| No. of studies | Quality assessment | | | | | | No. of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Doppler guidance | Anatomical landmarks | Relative (95% CI) | Absolute (95% CI) | | |
| Complication rate total | | | | | | | | | | | | |
| 3 | Randomised trials | Not serious | Not serious | Not serious | Serious[a] | None | 3/46 (6.5%) | 7/47 (14.9%) | RR 0.52 (0.16 to 1.71) | 71 Fewer per 1,000 (from 106 more to 125 fewer) | ⊕⊕⊕◯ Moderate | Critical |
| Overall success rate | | | | | | | | | | | | |
| 7 | Randomised trials | Not serious | Serious[b] | Not serious | Serious[a] | None | 128/139 (92.1%) | 120/150 (80.0%) | RR 1.09 (0.95 to 1.25) | 72 More per 1,000 (from 40 fewer to 200 more) | ⊕⊕◯◯ Low | Critical |
| Number of attempts until success | | | | | | | | | | | | |
| 2 | Randomised trials | Not serious | Serious[b] | Not serious | Serious[a] | None | 34 | 35 | – | MD 0.63 min lower (1.92 lower to 0.66 higher) | ⊕⊕◯◯ Low | Important |
| Arterial puncture | | | | | | | | | | | | |
| 6 | Randomised trials | Not serious | Not serious | Not serious | Serious[a] | None | 4/106 (3.8%) | 8/107 (7.5%) | RR 0.61 (0.21 to 1.73) | 29 Fewer per 1,000 (from 55 more to 59 fewer) | ⊕⊕⊕◯ Moderate | Critical |
| Time to successful cannulation | | | | | | | | | | | | |
| 5 | Randomised trials | Not serious | Not serious | Not serious | Serious[a] | None | 99 | 115 | – | MD 62.04 min higher (13.47 lower to 137.55 higher) | ⊕⊕⊕◯ Moderate | Important |
| Success with attempt number 1 | | | | | | | | | | | | |
| 4 | Randomised trials | Not serious | Not serious | Not serious | Not serious | None | 61/94 (64.9%) | 41/105 (39.0%) | RR 1.58 (1.02 to 2.43) | 226 More per 1,000 (from 8 more to 558 more) | ⊕⊕⊕⊕ High | Important |

[a], The 95% CI overlapped the null effect; [b], there is significant heterogeneity ($I^2$ >50%; P<0.05). CI, confidence interval; RR, risk ratio; MD, mean difference.

**Table 6** Real-time ultrasound guidance compared to landmark technique for central venous catheter insertion in pediatric patients

| No. of studies | Quality assessment | | | | | | No. of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Real-time ultrasound guidance | Landmark technique | Relative (95% CI) | Absolute (95% CI) | | |
| Successful CVC placement | | | | | | | | | | | | |
| 8 | Randomised trials | Serious[a] | Serious[b] | Not serious | Not serious | None | 338/377 (89.7%) | 268/391 (68.5%) | RR 1.318 (1.101 to 1.576) | 218 More per 1,000 (from 69 more to 395 more) | ⊕⊕◯◯ Low | Critical |
| Number of attempts required | | | | | | | | | | | | |
| 5 | Randomised trials | Serious[a] | Serious[b] | Not serious | Not serious | None | 226 | 228 | – | MD 1.261 attempts lower (1.711 lower to 0.812 lower) | ⊕⊕◯◯ Low | Important |
| Accidental arterial puncture | | | | | | | | | | | | |
| 8 | Randomised trials | Serious[a] | Serious[b] | Not serious | Serious[c] | None | 17/367 (4.6%) | 66/393 (16.8%) | RR 0.359 (0.118 to 1.093) | 108 fewer per 1,000 (from 16 more to 148 fewer) | ⊕◯◯◯ Very low | Important |
| Time to cannulation | | | | | | | | | | | | |
| 4 | Randomised trials | Serious[a] | Serious[b] | Not serious | Serious[c] | None | 138 | 153 | – | MD 1.123 min lower (2.6 lower to 0.353 higher) | ⊕◯◯◯ Very low | Important |

[a], The Jadad score was mostly 2–3 points for included studies; [b], there was significant heterogeneity between trials ($I^2$>50%; P<0.05); [c], the 95% CI: included the RR =1 line. CI, confidence interval; RR, risk ratio; MD, mean difference.

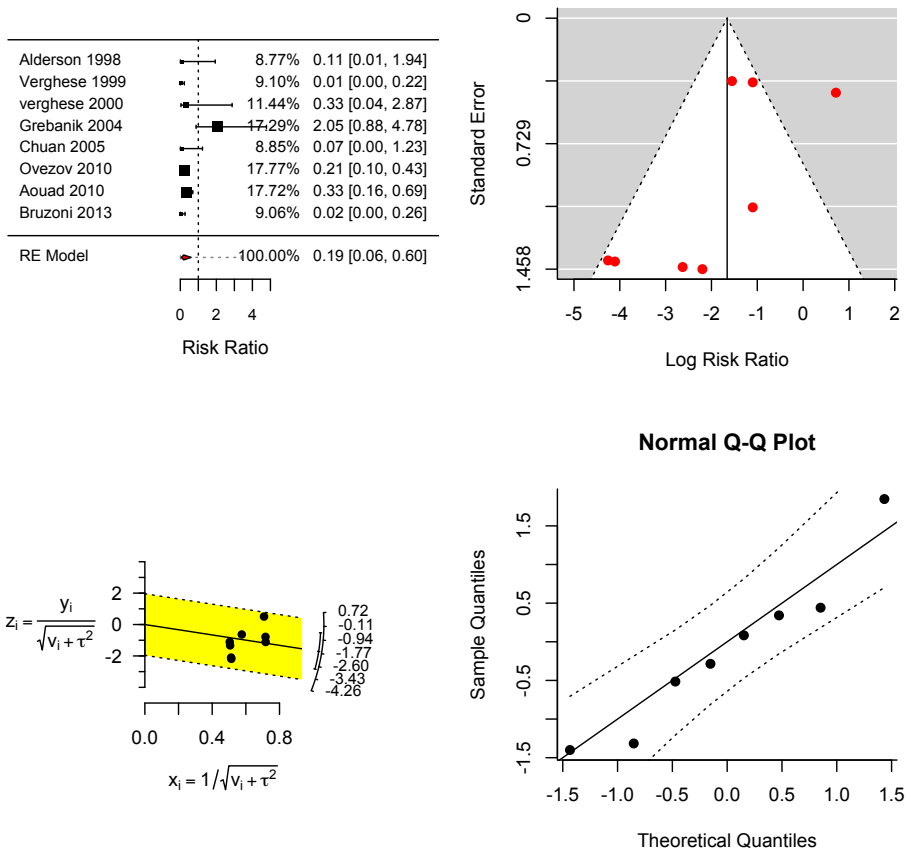


**Figure 1** Relative risk of failed CVC insertion in children. The forest plot showed that real-time ultrasound guided CVC insertion was able to reduce the risk of CVC insertion failure (RR 0.19; 95% CI: 0.06–0.60). However, the quality of evidence was downgraded due to imprecision and potential publication bias (funnel plot). The radial plot was used to examine heterogeneity among component trials. The vertical axis corresponds to standardized values, it is referred to as the z-axis within this function. The arc on the right corresponds to the individual observed effect sizes. A line projected from the point (0,0) through a particular point within the plot onto this arc indicates the value of the individual observed relative risk for that point. The extent of heterogeneity can be examined by vertical scatter of points in the plot. The normal QQ plot was to examine whether component studies were from a single population and potential publication bias. All studies were within the 95% confidence limit, indicating that all studies were from the same population. CVC, central venous catheter.

### *We suggest the use contrast-enhanced ultrasound (CEUS) for the confirmation of central venous catheter placement (2B)*

There were no RCTs directly investigating the impact of CEUS on patient-important outcomes. Thus, the potential influence of CEUS was inferred from the diagnostic accuracy of the test, and potential impact of false positive (FP), true positive (TP), false negative (FN) and true negative (TN) on patient-important outcomes (37,38). For all these types of outcomes, we considered FP as critical importance because FP may prompt changing or repositioning of the catheter. Changing catheter carries all risks associated with CVC insertion such as pneumothorax, artery injury and hemorrhage. Thus, a good diagnostic tool should low the risk rate of FP.

Systematic search identified a systematic review and meta-analysis published in 2017 (39). The study included 5 original studies exploring the diagnostic accuracy of CEUS in confirming CVC placement (40-44). A total of 572 patients were included, and the pooled sensitivity and specificity were 72% (95% CI: 44–91%) and 100% (99–100%), respectively. The FP rate was 0.5% in the overall studies. However, there is no RCT directly investigating the impact of CEUS on patient-important outcomes such as mortality, hemorrhage, blood stream infection and thrombosis. Furthermore, the cost of CEUS was high and

 

**Table 7** Evidence profiles for the question of Heparin versus normal saline for maintaining CVC patency

| No. of studies | Quality assessment | | | | | | No. of patients | | Effect, relative (95% CI) | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Heparin | Normal saline | | | |
| Catheter occlusion | | | | | | | | | | | |
| 12 | RCT | Low 1 | Not serious | Not serious | Not serious | None | 180/4,028 | 158/3,847 | RR 1.21 (0.91–1.61) | ⊕⊕⊕⊕ High | Moderate |
| Maneuver needed | | | | | | | | | | | |
| 2 | RCT | Low 1 | Serious | Not serious | Serious | None | 20/99 | 16/97 | RR 1.24 (0.71–2.16) | ⊕⊕⊕◯ Moderate | Moderate |
| Heparin-induced thrombocytopenia | | | | | | | | | | | |
| 2 | RCT | Low 1 | Not serious | Not serious | Serious | Publication bias | 2/636 | 1/627 | RR 1.33 (0.09–18.54) | ⊕⊕◯◯ Low | Critical |
| Haemorrhage | | | | | | | | | | | |
| 3 | RCT | Low 1 | Not serious | Not serious | Not serious | None | 8/225 | 10/214 | RR 0.75 (0.32–1.74) | ⊕⊕⊕⊕ High | Critical |

CI, confidence interval; RR, risk ratio; CVC, central venous catheter; RCT, randomized controlled trial.

CEUS carries potential risks of contrast agent allergy. Thus, we make a weak recommendation for the use of CEUS to confirm CVC placement (*Table 8*).

### *We recommend the use of bedside ultrasound together with agitated or non-agitated normal saline to confirm CVC position (1C)*

Since the CEUS is expensive and its impact on patient-important outcomes is unclear, the use of bedside ultrasound without contrast agents can also be used for the confirmation of catheter position in vascular and cardiac views. Normal saline with and without agitation can be used to, but is not mandatory, facilitate the identification of the catheter. There were numerous cohort studies being performed in this field (42,45-52), which has been summarized in a systematic review and meta-analysis (53). A total of 15 studies with 1,553 CVC insertions were identified, which resulted in a pooled sensitivity and specificity of catheter malposition by ultrasound of 0.82 (95% CI: 0.77–0.86) and 0.98 (95% CI: 0.97–0.99), respectively, corresponding to pooled positive and negative likelihood ratios of 31.12 (14.72–65.78) and 0.25 (0.13-0.47), respectively (*Table 9*). The diagnostic of ultrasound for pneumothorax detection was nearly 100% in the participating studies. The mean time required for bedside ultrasound confirmation of CVC was 5.6 minutes, which was significantly shorter than a time to chest radiograph completion of 63.9 minutes and a mean time to interpretation of 143.4 minutes. The quality of evidence was downgraded due to high risk of bias and clinical heterogeneity. Again, there was no RCT directly examining the impact of bedside ultrasound on patient-important outcomes such as mortality, pneumothorax requiring chest tube insertion and catheter malfunction (*Table 10*).

### *We suggest using subclavian site for CVC insertion (2C)*

The three major sites for CVC insertion are internal jugular, femoral and subclavian sites. The choices of the insertion sites have been studied in many clinical trials. There were two RCTs and approximately 10 cohort studies being conducted in this field (54-56). A systematic review and meta-analysis was identified from the literature, investigating the impact of CVC insertion site on the risk of CRBSI (57). The results of systematic review are shown in *Table 5*. The femoral site showed similar risk of CRBSI as that of subclavian site, and the evidence was considered as of very low quality because

 

**Table 8** Quality assessment of diagnostic accuracy of CEUS

| No. of studies [patients] | Quality assessment | | | | | | No. of patients (%) | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | Sen. (95% CI) | Spe. (95% CI) | | |
| TP (patients correctly classified as with CVC malposition) | | | | | | | | | | | |
| 5 [572] | Observational | Low 1 | Serious | Not serious | Not serious | None | 35 (6.0) | 72% (44–91%) | 100% (99–100%) | ⊕⊕⊕◯ Moderate | Moderate |
| FP (patients incorrectly classified as with CVC malposition) | | | | | | | | | | | |
| 5 [572] | Observational | Low 1 | serious | Not serious | Not serious | None | 3 (0.5) | 72% (44–91%) | 100% (99–100%) | ⊕⊕⊕◯ Moderate | Critical |
| FN (patients incorrectly classified as without CVC malposition) | | | | | | | | | | | |
| 5 [572] | Observational | Low 1 | serious | Not serious | Not serious | None | 8 (1.4) | 72% (44–91%) | 100% (99–100%) | ⊕⊕⊕◯ Moderate | Moderate |
| TN (patients correctly classified as without CVC malposition) | | | | | | | | | | | |
| 5 [572] | Observational | Low 1 | Serious | Not serious | Not serious | None | 526 (92.0) | 72% (44–91%) | 100% (99–100%) | ⊕⊕⊕◯ Moderate | Low |

CEUS, contrast-enhanced ultrasound; CI, confidence interval; RR, risk ratio; CVC, central venous catheter; RCT, randomized controlled trial; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

**Table 9** Evidence profile on the question should bedside ultrasound be used to diagnose CVC position in critically ill patients with CVC

| Outcome | No. of studies (No. of patients) | Study design | Factors that may decrease quality of evidence | | | | | Effect per 1,000 patients tested, pre-test probability of 17.6% | Test accuracy QoE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | | |
| TPs (patients with CVC position) | 13 Studies (1,469 patients) | Cohort & case-control type studies | Not serious | Not serious | Serious[a] | Not serious | None | 144 (136 to 151) | ⊕⊕⊕◯ Moderate |
| FNs (patients incorrectly classified as not having CVC position) | | | | | | | | 32 (25 to 40) | |
| TNs (patients without CVC position) | 13 studies (1,469 patients) | Cohort & case-control type studies | Not serious | Not serious | Serious[a] | Not serious | None | 808 (799 to 816) | ⊕⊕⊕◯ Moderate |
| FPs (patients incorrectly classified as having CVC position) | | | | | | | | 16 (8 to 25) | |

Sensitivity, 0.82 (95% CI: 0.77 to 0.86); specificity, 0.98 (95% CI: 0.97 to 0.99); prevalences, 17.6%. [a], There was large heterogeneity among included studies ($I^2$ >50%; P<0.05). CI, confidence interval; RR, risk ratio; CVC, central venous catheter; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

**Table 10** Summary of judgements on the question should bedside ultrasound be used to diagnose CVC position in critically ill patients with CVC

| Aspects | Judgement | | | | | | | Implications |
|---|---|---|---|---|---|---|---|---|
| Problem | No | Probably no | Probably yes | Yes | – | Varies | Don't know | |
| Test accuracy | Very inaccurate | Inaccurate | Accurate | Very accurate | – | Varies | Don't know | |
| Desirable effects | Trivial | Small | Moderate | Large | – | Varies | Don't know | |
| Undesirable effects | Large | Moderate | Small | Trivial | – | Varies | Don't know | |
| Certainty of the evidence of test accuracy | Very low | Low | Moderate | High | – | – | No included studies | |
| Certainty of the evidence of test's effects | Very low | Low | Moderate | High | – | – | No included studies | |
| Certainty of the evidence of management's effects | Very low | Low | Moderate | High | – | – | No included studies | |
| Certainty of the evidence of test result/management | Very low | Low | Moderate | High | – | – | No included studies | |
| Certainty of effects | Very low | Low | Moderate | High | – | – | No included studies | |
| Values | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | No important uncertainty or variability | – | – | – | |
| Balance of effects | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know | |
| Resources required | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know | |
| Certainty of evidence of required resources | Very low | Low | Moderate | High | – | – | No included studies | |
| Cost effectiveness | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | No included studies | |
| Equity | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know | |
| Acceptability | No | Probably no | Probably yes | Yes | – | Varies | Don't know | |
| Feasibility | No | Probably no | Probably yes | Yes | – | Varies | Don't know | |

CVC, central venous catheter.

**Table 11** Evidence profiles for the insertion sites of central venous catheter (without considering the meta-trial)

| No. of studies | Quality assessment | | | | | | No. of patients[#] | | Effect, relative (95% CI) | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Site 1 | Site 2 | | | |
| CRBSI (femoral *vs.* subclavian) | | | | | | | | | | | |
| 8 | Cohort | High | Serious | Not serious | Not serious | None | 28/2,152 | 37/1,993 | RR 1.00 (0.61–1.62) | ⊕◯◯◯ Very low | Critical |
| 1 | RCT | High | Not serious | Not serious | Serious | None | 2/134 | 1/136 | RR 2.03 (0.19–22.12) | ⊕◯◯◯ Very low | Critical |
| CRBSI (femoral *vs.* internal jugular) | | | | | | | | | | | |
| 8 | Cohort | High | Serious | Not serious | Not serious | None | 80/2,684 | 92/10,592 | RR 2.16 (1.44–3.22) | ⊕⊕◯◯ Low | Critical |
| 1 | RCT | High | Not serious | Not serious | Serious | None | 3/370 | 5/366 | RR 0.59 (0.14–2.47) | ⊕⊕◯◯ Low | Critical |
| DVT (femoral *vs.* subclavian/internal jugular) | | | | | | | | | | | |
| 2 | RCT | Low | Serious | Not serious | Serious | None | 33/192 | 19/182 | RR 2.20 (0.07–64.73) | ⊕◯◯◯ Very low | Critical |
| Mechanical complications (internal jugular *vs.* subclavian) | | | | | | | | | | | |
| 2 | RCT | Low 1 | Not serious | Serious | Not serious | None | 3/232 | 3/236 | RR 1.00 (0.21–4.84) | ⊕◯◯◯ Very low | Moderate |

[#], Site 1 and site 2 represent the sites listed in the outcome row. The first site in the row was site 1 and the second site was site 2. CI, confidence interval; RR, risk ratio; CRBSI, catheter-related blood stream infection; RCT, randomized controlled trial; DVT, deep vein thrombosis.

of serious inconsistency and imprecision. While RCT did not report difference on the risk of CRBSI for femoral versus internal jugular veins, cohort studies showed higher risk of CRBSI in femoral versus internal jugular veins (RR 2.16; 95% CI: 1.44–3.22). With respect to the deep vein thrombosis (DVT), there was no significant difference in femoral versus subclavian/internal jugular veins. Two RCTs investigated mechanical complications of CVC influenced by insertion site (58,59). When internal jugular vein was compared with the SV, there was no difference in mechanical complications (RR 1.00; 95% CI: 0.21–4.84) (60). The evidence was downgraded by serious indirectness because one study enrolled patients requires chemotherapy (58). A recent mega-trial involving 3,027 patients showed that there were 8, 20, and 22 primary CRBSIs in the subclavian, jugular, and femoral groups, respectively (1.5, 3.6, and 4.6 per 1,000 catheter-days; P=0.02) (61). When the three arms were compared in pairwise fashion, the femoral group had significantly higher risk of CRBSI than that in the subclavian group (hazard ratio, 3.5; 95% CI, 1.5–7.8; P=0.003), and the jugular group had higher risk than that in the subclavian group (HR: 2.1; 95% CI, 1.0–4.3; P=0.04). However, the subclavian group showed higher rate of pneumothorax requiring chest tube insertion. A recent meta-analysis updated in 2017 showed that internal jugular (RR 2.25; 95% CI: 1.84–2.75; $I^2$ =0%) and femoral (RR 2.92; 95% CI: 2.11–4.04); $I^2$ =24%) had higher risk of colonization as compared with subclavian site (62). CRBSI was comparable for internal jugular and subclavian. Femoral site had higher risk of CRBSI than subclavian (RR 2.44; 95% CI: 1.25–4.75; $I^2$ =61%), and internal jugular had lower risk of CRBSI than femoral (RR 0.55; 95% CI: 0.34–0.89; $I^2$ =61%). Due to the benefit and risk of subclavian insertion site, we make a weak recommendation for it (*Table 11*).

However, the choice of insertion site must be balanced with the experience of the operator and the clinical situation. User experience of the different sites of insertion will have a profound effect on the safest route in any given situation, balancing the complications of insertion with the complications over time related to the site of insertion. For example, anesthetists may become very proficient in the use of internal jugular

 

**Table 12** Evidence profiles for the prevention of CVC-related DVT in children

| No. of studies | Quality assessment | | | | | | No. of patients[#] | | Effect, relative (95% CI) | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Site 1 | Site 2 | | | |
| Heparin-bonded CVC *vs.* control | | | | | | | | | | | |
| 2 | RCT | Low | Serious | Serious | Serious | None | 21/144 | 26/143 | RR 0.34 (0.01–7.68) | ⊕◯◯◯ Very low | Critical |
| Unfractionated heparin *vs.* control | | | | | | | | | | | |
| 4 | RCT | Low | Not serious | Serious | Serious | None | 27/177 | 26/164 | RR 0.93 (0.57–1.51) | ⊕⊕◯◯ Low | Critical |
| Low molecular heparin *vs.* control | | | | | | | | | | | |
| 1 | RCT | Low | Serious | Not serious | Serious | None | 11/78 | 10/80 | RR 1.13 (0.51–2.50) | ⊕◯◯◯ Very low | Critical |
| Warfarin *vs.* control | | | | | | | | | | | |
| 1 | RCT | Low 1 | Not serious | Serious | Not serious | None | 6/29 | 8/33 | RR 1.00 (0.34–2.17) | ⊕◯◯◯ Very low | Critical |
| Antithrombin concentrate *vs.* control | | | | | | | | | | | |
| 1 | RCT | Low 1 | Not serious | Serious | Not serious | None | 7/25 | 22/60 | RR 0.76 (0.38–1.55) | ⊕◯◯◯ Very low | Critical |
| Nitroglycerin *vs.* control | | | | | | | | | | | |
| 1 | RCT | Low 1 | Not serious | Serious | Not serious | None | 7/21 | 5/23 | RR 1.53 (0.57–4.10) | ⊕◯◯◯ Very low | Critical |

[#], Site 1 and site 2 represent the sites listed in the outcome row. The first site in the row was site 1 and the second site was site 2. The outcome is the same for all comparisons. CI, confidence interval; RR, risk ratio; RCT, randomized controlled trial; DVT, deep vein thrombosis; CVC, central venous catheter.

catheterization because of the nature and access of this site during surgery and the inability of excluding possible pneumothorax following placement in the operating room. Additionally, ultrasound assisted insertion is easier taught for the internal jugular site and for many insertions this will be of necessity performed by junior doctors within their learning curve.

### *We suggest not using heparin-bonded catheters or warfarin to prevent CVC-related DVT in children (2D)*

One important complication of CVC is the DVT. When the thrombus detached from the CVC insertion site, it can cause pulmonary embolism. The latter medical condition can be life-threatening. Pediatric patients are a specific group of population that need attention. Up to date, there are several RCTs investigating strategies to prevent DVT in children (63-72). These strategies included heparin-bounded CVC, unfractionated heparin, low molecular heparin, warfarin, antithrombin concentrate and nitroglycerin (73). However, none of these strategies were found to be able to reduce the risk of DVT (*Table 6*). Many of these included studies were not conducted in the ICU (65-68,72), compromising its directness to inform ICU staffs. Overall, the evidence underlying the DVT prevention was considered to be very low and we suggest not using these strategies or drugs to prevent DVT in children (*Table 12*).

### *We recommend the implementation of central-line bundles to reduce the risk of CRBSI for adult, pediatric and neonatal ICUs (1B)*

Since the presence of CVC has been identified as an important risk factor for CRBSI, implementation of central-line bundles is important to reduce the relative risk. There

 

is no definitive consensus on specific procedures of central-line bundles and large variations exist across studies. A complete central-line bundle includes insertion bundle and maintenance bundle. The former included maximum barrier precaution (handwashing, wearing a cap, mask, sterile gown and gloves), skin-cleaning with chlorhexidine or povidone ionide, complete CVC cart that contain all necessary supplies for insertion a CVC, hand hygiene, Sterile dressing or gauze, use of CVC insertion checklist, Optimal CVC site (e.g., avoid femoral vein in adult). The latter includes Hand hygiene, Needle free connector, Infusion sets labeled, Replacement sets in predefined interval, label date of CVC insertion, Handling of CVC with sterile gauze-alcohol solution (74-81). In patients not receiving blood, blood products or fat emulsions, replace administration sets that are continuously used, including secondary sets and add-on devices, no more frequently than at 96-hour intervals, but at least every 7 days (82). Category IA (PMID: 21511081) Replace tubing used to administer blood, blood products, or fat emulsions (those combined with amino acids and glucose in a 3-in-1 admixture or infused separately) within 24 hours of initiating the infusion (82). Replace tubing used to administer propofol infusions every 6 or 12 hours, when the vial is changed, per the manufacturer <publication> <uuid> A85CC08A-BFA1-4583-BF (82). Administration sets for blood and blood components should be changed when the transfusion episode is complete or every 12 h (whichever is sooner); administration sets used for lipid-containing parenteral nutrition should be changed every 24 h (36). In clinical practice, several components are essential for the successful implementation of central-line bundle. (I) leadership refers to leaders at any level of the organization who have a direct and indirect influence on the implementation of CVC-bundles; (II) opinion leader is a health professionals nominated by their colleagues as 'educationally influential', whose role is to openly take the position in support of the intervention being implemented; (III) protocol is recommended pathways for the successful implementation of CVC bundles; (IV) educational outreach refers to the provision of evidence-based information about best prescribing practices by a health educator to physicians; (V) checklist is a set of items that should be checked off at the point of care; (VI) remainder refers to any interventions, provided verbally, on paper, or computerized, which are intended to prompt clinicians to take clinical action in keeping with the CVC bundles; (VII) feedback and audit refers to the collection of data regarding the performance of CVC bundles; and (VIII) education can be a forum or session in which knowledge of CVC bundles are delivered.

An updated systematic review and meta-analysis involving 79 original studies was included for making the recommendation (83). Most of the 79 studies were before-and-after study that the prevalence of CRBSI was compared before and after the implementation of CVC bundles. When data from all 79 studies were pooled with a random-effects model, the incidence risk ratio was 0.44 (95% CI: 0.39–0.50) favoring the bundle group. Similar results were obtained in adult ICU (IRR 0.45; 95% CI: 0.39–0.52), pediatric ICU (IRR 0.58; 95% CI: 0.48–0.71) and neonate ICU (IRR 0.47; 95% CI: 0.38–0.59). There were two clustered RCTs having been conducted. Speroff T and colleagues reported that the CLABSI rate was 2.42 per 1,000 catheter days at baseline and 2.73 at 18 months (P=0.59) (84). A clustered RCT enrolling 45 ICUs reported that while the baseline CRBSI rate was comparable between the intervention and control group (4.48 *vs.* 2.71 per 1,000 central line days; P=0.28), the infection rate declined to 1.33 in the intervention group compared to 2.16 in the control group (incidence rate ratio 0.19; P=0.003; 95% CI: 0.06–0.57) (85). Because there was significant heterogeneity among component studies ($I^2$ =89% for all ICUs, 67%, 18% and 18% for adult, pediatric and neonate ICUs, respectively), and nearly all these studies were not RCT, the grade of evidence was downgraded to moderate (B). However, due to potential benefits and risks of bundle implementation, all experts believed the bundle implementation should be strongly recommended.

### *We suggest skin antisepsis with chlorhexidine throughout in-dwelling period for reducing CVC-related infections (2D)*

It is proposed that the CVC-related infections are caused by insertion site contamination, and the following colonization on external surface of the catheter. Thus, it is rationale to deduce that skin antisepsis throughout the in-dwelling period can be effective in reducing CVC-related infections. Many RCTs have been conducted to investigate whether skin antisepsis was effective in reducing CVC-related infection (86-94). The three major antiseptic agents reported in the literature are chlorhexidine, iodine and alcohol. Antiseptic agents were applied both before catheter insertion and regularly thereafter during the in-dwelling period. The frequency of skin cleansing ranged from 24 to 72 h across these studies.

These studies were summarized in a systematic review

 

**Table 13** Evidence profile for the effectiveness of povidone-iodine (in aqueous solution) compared to no skin antisepsis for patients with CVC

| No. of studies | Quality assessment | | | | | | No. of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Povidone-iodine (in aqueous solution) | No skin antisepsis | Relative (95% CI) | Absolute (95% CI) | | |
| Catheter-related BSI | | | | | | | | | | | | |
| 1 | Randomised trials | Serious[a] | Not serious | Not serious | Serious[b] | None | 7/84 (8.3%) | 8/95 (8.4%) | RR 0.99 (0.37 to 2.61) | 1 Fewer per 1,000 (from 53 fewer to 136 more) | ⊕⊕◯◯ Low | Critical |
| Catheter colonisation | | | | | | | | | | | | |
| 1 | Randomised trials | Serious[a] | Not serious | Not serious | Serious[b] | None | 18/84 (21.4%) | 22/95 (23.2%) | RR 0.93 (0.53 to 1.60) | 16 Fewer per 1,000 (from 109 fewer to 139 more) | ⊕⊕◯◯ Low | Not important |

[a], Allocation concealment, blinding of participants and personnel were at high risk. Also, there was a unit of analysis issue in which the number of catheters analysed exceeded the number of participants by nearly 10%, and the outcomes were reported using catheters as the units; [b], the 95% CI: included the null effect line. CI, confidence interval; RR, risk ratio; CVC, central venous catheter.

**Table 14** Evidence profile for Chlorhexidine (in aqueous solution) compared to no skin antisepsis for patients with CVC

| No. of studies | Quality assessment | | | | | | No. of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Chlorhexidine (in aqueous solution) | No skin antisepsis | Relative (95% CI) | Absolute (95% CI) | | |
| Septicaemia | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Very serious[a] | None | 3/69 (4.3%) | 1/67 (1.5%) | RR 2.91 (0.31 to 27.31) | 29 more per 1,000 (from 10 fewer to 393 more) | ⊕⊕◯◯ Low | Important |
| Catheter colonisation | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Very serious[a] | None | 13/60 (21.7%) | 11/64 (17.2%) | RR 1.26 (0.61 to 2.59) | 45 More per 1,000 (from 67 fewer to 273 more) | ⊕⊕◯◯ Low | Not important |
| Number of patients who required antibiotics during in-dwelling period of catheter | | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Not serious | Very serious[a] | None | 25/69 (36.2%) | 29/67 (43.3%) | RR 0.84 (0.55 to 1.27) | 69 Fewer per 1,000 (from 117 more to 195 fewer) | ⊕⊕◯◯ Low | Important |

[a], The 95% CI: overlapped null effect line and the optimal information size was not reach the target value. CI, confidence interval; RR, risk ratio; CVC, central venous catheter.

**Table 15** Evidence profile for Chlorhexidine compared to povidone-iodine in patients with CVC

| No. of studies | Quality assessment | | | | | | No. of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Chlorhexidine | Povidone-iodine | Relative (95% CI) | Absolute (95% CI) | | |
| Catheter-related BSI | | | | | | | | | | | | |
| 5 | Randomised trials | Serious[a] | Not serious | Not serious | Not serious | None | 41/838 (4.9%) | 38/598 (6.4%) | RR 0.64 (0.41 to 0.99) | 23 Fewer per 1,000 (from 1 fewer to 37 fewer) | ⊕⊕⊕◯ Moderate | Critical |
| All-cause mortality | | | | | | | | | | | | |
| 1 | Randomised trials | Serious[a] | Not serious | Not serious | Serious[b] | None | 22/116 (19.0%) | 25/106 (23.6%) | RR 0.80 (0.48 to 1.34) | 47 Fewer per 1,000 (from 80 more to 123 fewer) | ⊕⊕◯◯ Low | Critical |
| Catheter colonisation | | | | | | | | | | | | |
| 6 | Randomised trials | Serious[a] | Not serious | Not serious | Not serious | None | 146/883 (16.5%) | 156/650 (24.0%) | RD −0.08 (−0.12 to −0.03) | 75 per 1,000 (from 30 to 120) | ⊕⊕⊕◯ Moderate | Not important |
| Insertion site infection | | | | | | | | | | | | |
| 1 | Randomised trials | Serious[c] | Not serious | Not serious | Serious[b] | None | 125 | 117 | – | MD 2.8 CFU lower (9.1 lower to 3.5 higher) | ⊕⊕◯◯ Low | Critical |

[a], A study employed a block randomisation schedule with high likelihood that blinding of participants and personnel were not achieved. This posed a risk to the integrity of the random sequence, which would be vulnerable to disruption following educated guesses by those involved in the study on the likely assigned group of the future participants There was a serious unit of analysis issue in which the number of catheters analysed exceeded the number of participants by over 50%, and the major outcomes were reported using catheters as the units; [b], the 95% CI: included the RR =1 line and the OIS was not reached; [c], high risk in terms of Blinding of participants and personnel and Incomplete outcome data (attrition bias). Others: the study employed a block randomisation schedule with high likelihood that blinding of participants and personnel could not be achieved. This posed a risk to the integrity of the random sequence which would be vulnerable to disruption following educated guesses by those involved in the study on the likely assigned group of the future participants. CI, confidence interval; RR, risk ratio; MD, mean difference; CVC, central venous catheter; RD, risk difference; CFU, colony-forming unit.

**Table 16** Evidence profile for Chlorhexidine (in aqueous solution) compared to alcohol for patients with CVC

| No. of studies | Quality assessment | | | | | | No. of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Chlorhexidine (in aqueous solution) | Alcohol | Relative (95% CI) | Absolute (95% CI) | | |
| Catheter related BSI | | | | | | | | | | | | |
| 1 | Randomised trials | Serious[a] | Not serious | Not serious | Serious[b] | None | 1/67 (1.5%) | 2/32 (6.3%) | RR 0.24 (0.02 to 2.54) | 48 Fewer per 1,000 (from 61 fewer to 96 more) | ⊕⊕◯◯ Low | Critical |
| Catheter colonisation | | | | | | | | | | | | |
| 1 | Randomised trials | Serious[a] | Not serious | Not serious | Serious[b] | None | 4/67 (6.0%) | 5/32 (15.6%) | RR 0.38 (0.11 to 1.33) | 97 Fewer per 1,000 (from 52 more to 139 fewer) | ⊕⊕◯◯ Low | Not important |

[a], High risk of blinding: "Although it was not possible for the users or the research nurses to be blinded to the antiseptic agent used …"; [b], OIS not reached and the 95% CI: overlap the null effect line. CI, confidence interval; RR, risk ratio; CVC, central venous catheter.

and meta-analysis (95). A total of 13 studies were eligible for the analysis (*Tables 13-16*). The overall quality of included studies was considered to be low. Study endpoints such as catheter-related BSI, septicaemia, catheter colonisation and number of patients who required systemic antibiotics were not significantly different among all these agents. There was weak evidence (the level of evidence was downgraded due to imprecision and the risk of bias) that chlorhexidine may reduce the risk of CRBSI [RR of 0.64, 95% CI: 0.41–0.99; absolute risk reduction (ARR) 2.30%, 95% CI: 0.06–3.70%] and catheter colonization (RR of 0.68, 95% CI: 0.56–0.84; ARR 8%, 95% CI: 3–12%; 5 studies involving 1,533 catheters, downgraded for indirectness, risk of bias and inconsistency) as compared with povidone-iodine. Other head-to-head comparisons such as alcoholic chlorhexidine versus aqueous povidone-iodine, aqueous chlorhexidine versus aqueous povidone-iodine and alcoholic chlorhexidine versus alcoholic povidone-iodine showed no clear difference in CRBSI and mortality (95). In conclusion, the evidence is very low and skin antisepsis with chlorhexidine may provide protective effect against catheter colonization and CRBSI.

### *We recommend a differential time to positivity (DTP) of blood cultures from CVC and peripheral vein of 120 minutes to diagnose CRBSI (1B)*

CRBSI is an important cause of morbidity and mortality and is potentially preventable. One challenge in the management of CRBSI is the correct diagnosis. In a critically ill patient with suspected infection, CRBSI should be suspected in the presence of a CVC. Blood samples should be sent for blood cultures. There is plenty of evidence showing that a DTP of blood cultures of 120 minutes has high sensitivity and specificity in diagnosing CRBSI. García and colleagues used DTP >120 min as a cutoff point, and correctly diagnosed 12 out of 15 CR-BSI cases (sensitivity 80%, specificity 99%, PPV 92%, NPV 98%) (96). Similar results were replicated in other studies (97-99). However, there is lack of evidence that such a high accuracy can be translated to benefits of patient important outcomes.

## Editorial independence

There was no fund for the guideline development, and the members of the guideline development group declared no conflict of interest. The guideline was reviewed by

 

independent reviewers.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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