of septic shock. Vasopressors have been traditionally administered via a central venous access due to concerns of extravasation, local tissue ischaemia and injury if administered peripherally. However, the process of securing central venous access can be time consuming and requires specialised equipment and training that may not be available in under resourced settings even in high income countries, leading to a delayed initiation of vasopressors [385]. Large randomised trials that compare central and peripheral catheters for initial infusion of vasopressor are lacking. A small study ($n=263$) randomly allocated patients to receive peripheral vascular access or a central access [386]. The need for vasopressor was the indication for venous access in 70% of the patients. The incidence of major catheter-related complications was higher in those randomised to peripheral venous lines with no significant difference in the incidence of minor catheter-related complication. The most common peripheral venous line complication was difficulty in placement. Almost half of the patients assigned to the peripheral access group did not need a central line throughout their ICU stay. Other authors also showed that central lines could be avoided by peripheral line insertion [387]. The administration of vasopressors through peripheral IV catheters is generally safe. A recent systematic review showed that extravasation occurred in 3.4% (95% CI 2.5–4.7%) of patients with no reported episodes of tissue necrosis or limb ischaemia [388]. Most of the studies reported no need for active treatment of the extravasation, and a systematic review concluded that most patients who experience extravasation events have no long-term sequelae [389]. Extravasation may occur more frequently if vasopressors are infused distally to the antecubital fossa; a meta-analysis showed that 85% of reported extravasation events occurred when vasopressors were infused by a catheter that was located distal to the antecubital fossa [389]. The occurrence of local tissue injury may be more likely with prolonged administration of vasopressors. Administration of vasopressors for a short period of time (< 6 h) in a well-placed peripheral catheter proximal to the antecubital fossa is unlikely to cause local tissue injury [389].

The time to initiation of vasopressors may be shorter if peripheral access is used. A post-hoc analysis of the ARISE trial showed that 42% of patients had vasopressors initiated via a peripheral catheter with a shorter time to initiation of vasopressors (2.4 [1.3–3.9] vs. 4.9 h [3.5–6.6], $p<0.001$) [385]. Moreover, most patients who had vasopressors started peripherally achieved a MAP > 65 mmHg within 1 h. Delay in vasopressor initiation and achieving MAP of 65 is associated with increased mortality [390, 391].

Given the low complication rate of peripheral vasopressors and the possibility of restoring blood pressure faster, the benefits of initiating vasopressors for a short period of time in a vein proximal to the antecubital fossa probably outweigh the risks. Therefore, we issued a weak recommendation in favour of the rapid initiation of vasopressors peripherally. If the infusion of vasopressors is still needed after a short period of time, as soon as practical and if resources are available, they should be infused through a central venous access to minimise the risk of complications. The lack of availability and expertise in placement of central venous catheters in different settings is an important consideration [55]. Though data are generally sparse on the latter, a study of mostly senior resident doctors in Nigeria concluded that knowledge of central venous catheter placement was limited [392]. Though the panel suggests peripheral administration of norepinephrine as a temporizing measure until a central venous catheter can be placed, its longer-term central administration may not be possible in some settings. Larger prospective studies are needed to provide better evidence on the adequacy and safety of peripheral lines in this scenario.

Fluid balance

Recommendation
45. There is **insufficient evidence to make a recommendation** on the use of restrictive versus liberal fluid strategies in the first 24 h of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after initial resuscitation
Remarks
Fluid resuscitation should be given only if patients present with signs of hypoperfusion

Rationale

The current literature does not provide clear guidance about the best fluid strategy following the initial resuscitation bolus of fluids. The four largest clinical trials in sepsis resuscitation used moderate to large amounts of fluids in the first 72 h. Although Rivers [393] administered over 13 L of fluids, ProCESS[64], ARISE [65] and ProMISe [66] administered approximately 7–8 L in the usual care groups with a reported low mortality rate. However, recent evidence suggests that IV fluids used to restore organ perfusion may damage vascular integrity and lead to organ dysfunction [394]. Data from observational studies have shown an association of high-volume fluid resuscitation and increased mortality, but these studies are likely affected by unmeasured variables (i.e. the administration of higher amounts of fluids to sicker patients) [395, 396]. Recent data emerging from Africa showed that higher volume fluid resuscitation in adults was associated with