

increased mortality, but the generalizability of these data is limited due to the high prevalence of HIV/AIDS and malnutrition in the patients enrolled and the resource-scarce conditions with limited access to ICUs [69].

The current evidence evaluating a restrictive IV fluid strategy in the management of septic patients varies with respect to the inclusion criteria, the definition of restrictive and liberal fluid strategies, the criteria guiding the administration of additional IV fluids (e.g., perfusion parameters vs. haemodynamic variables), and the duration of the interventions [397–401]. Moreover, the primary outcomes were mostly related to IV fluid volumes administered during the study period and given the small sample sizes, they were not powered to identify differences in patient-centered outcomes. The ongoing Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial and the Conservative vs liberal fluid therapy in septic shock (CLASSIC) trial will shed some light to this matter [402, 403]. Given the quality of the evidence and the variability among existing studies, the panel issued no recommendation for either restrictive or liberal fluid management in the first 24 h of resuscitation after the initial fluid bolus in patients with sepsis and septic shock. However, it is important to emphasise this discussion does not affect the recommendation for the initial IV fluid bolus and that the administration of IV fluids after the initial fluid bolus should be guided by perfusion parameters and not only by a response in haemodynamic variables.

Ventilation

Oxygen targets

Recommendation
46. There is insufficient evidence to make a recommendation on the use of conservative oxygen targets in adults with sepsis-induced hypoxemic respiratory failure

Rationale

Patients who are undergoing mechanical ventilation in the ICU often receive a high fraction of inspired oxygen and have a high arterial oxygen tension. The conservative use of oxygen may reduce oxygen exposure and diminish lung and systemic oxidative injury. The evidence for the use of conservative oxygen targets (generally defined as PaO₂ 55–70 mmHg; SpO₂ 88–92%) and therapy in patients with sepsis is limited, with three randomised trials in the critically ill population [404–406]. In the 1000-participant ICU-ROX trial [405], conservative oxygen therapy did not significantly affect the primary outcome, which was the number of ventilator-free days, compared with liberal oxygen therapy for ventilated adults in ICU. Mortality at 90 and 180 days did not differ. These findings are at variance with the results of a

previous single-centre trial, which was stopped early after an unplanned interim analysis. In that trial, conservative oxygen therapy in the ICU was associated with a markedly lower rate of death than usual oxygen therapy [404]. In a recent systematic review and meta-analysis of multiple clinical syndromes, investigators found that a conservative oxygen strategy was associated with a lower rate of death in acutely ill adults than a liberal oxygen strategy [407]. However, in a post hoc analysis of the ICU-ROX trial including adults with sepsis, point estimates for the treatment effect of conservative oxygen therapy on 90-day mortality raise the possibility of clinically important harm [408]. The LOCO-2 study was terminated early by the data safety and monitoring board and reported no difference in 28-day survival in ARDS patients managed with a conservative oxygenation strategy [409]. There are several ongoing trials of conservative oxygen targets that will inform clinical practice in the future. At this point in time, there is insufficient evidence to make an evidence-based recommendation.

High-flow nasal oxygen therapy

Recommendation
47. For adults with sepsis-induced hypoxemic respiratory failure, we suggest the use of high flow nasal oxygen over non-invasive ventilation <i>Weak recommendation, low quality of evidence</i>

Rationale

Acute hypoxemic respiratory failure can result from causes of sepsis such as pneumonia or non-pulmonary infections resulting in ARDS. Patients presenting with hypoxia without hypercapnia are treated with high concentrations of inhaled oxygen which may be delivered conventionally with interfaces including nasal prongs, facemask with reservoir or Venturi mask.

Advanced interventions for patients with severe hypoxia requiring escalation of support include non-invasive ventilation (NIV) or high flow oxygen. Both therapies avoid the complications of intubation and invasive mechanical ventilation and promote patient interaction. In addition to improving gas exchange, NIV may help to reduce work of breathing in select patients. However, NIV use can be associated with development of complications including increased risk of gastric insufflation and aspiration, facial skin breakdown, excessively high tidal volumes as well as patient discomfort related to inability to eat or effectively phonate during therapy.

High flow nasal cannula (HFNC) is a non-invasive, high concentration oxygen delivery interface that confers warming and humidification of secretions, high flow rates to better match patient demand, washout of nasopharyngeal dead space, and modest positive airway pressure