**Supplemental Digital Content**

**The Surviving Sepsis Campaign Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)**

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# Methodology

**Figure S1. Algorithm for using indirect evidence**



**Figure S2.** **Algorithm for interaction between indirectness and quality of evidence**



**Figure S3.** **Assessing indirectness of population**

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# Infection Control Questions:

**Table S1.** **PICO question: Recommendation 1**

|  |  |  |  |
| --- | --- | --- | --- |
| In healthcare workers performing **aerosol-generating procedures** on patients with COVID-19, should we recommend using fitted respirator mask, versus surgical/medical masks? | | | |
| Population | Intervention | Comparator | Outcomes |
| Healthcare workers performing aerosol-generating procedures | fitted respirator mask (N-95, FFP2, or equivalent) | Surgical/medical masks | 1. Disease transmission |

**Table S2. PICO question: Recommendation 2**

|  |  |  |  |
| --- | --- | --- | --- |
| In healthcare workers performing **aerosol-generating procedures** on ICU patients with COVID-19, should we recommend using negative pressure room, over regular room? | | | |
| Population | Intervention | Comparator | Outcomes |
| Healthcare workers performing aerosol-generating procedures | Negative pressure room | Regular room | 1. Disease transmission |

**Table S3. PICO question: Recommendation 3**

|  |  |  |  |
| --- | --- | --- | --- |
| In healthcare workers performing **caring for non-mechanically ventilated patients** with COVID-19, should we recommend using fitted respirator mask, versus surgical/medical masks? | | | |
| Population | Intervention | Comparator | Outcomes |
| Healthcare workers caring for non-mechanically ventilated patients (i.e. not on NIPPV, IMV, or HFNC) | Fitted respirator mask | Medical/surgical mask | 1. Disease transmission |

**Table S4. PICO question: Recommendation 4**

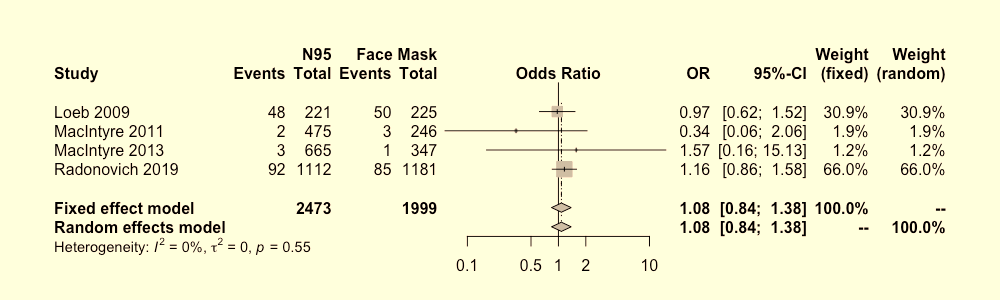
|  |  |  |  |
| --- | --- | --- | --- |
| In healthcare workers performing **non-aerosol-generating procedures** on mechanically ventilated patients with COVID-19, should we recommend using fitted respirator mask, versus surgical/medical masks? | | | |
| Population | Intervention | Comparator | Outcomes |
| Healthcare workers performing non-aerosol-generating procedures | Fitted respirator mask | Medical/surgical mask | 1. Disease transmission |

**Table S5. PICO question: Recommendation 5-6**

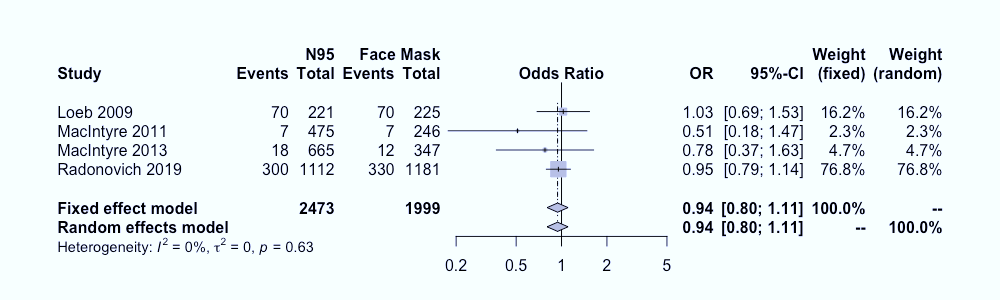
|  |  |  |  |
| --- | --- | --- | --- |
| In healthcare workers performing **endotracheal intubation** on patients with COVID-19, should we recommend using video guided laryngoscopy, over direct laryngoscopy? | | | |
| Population | Intervention | Comparator | Outcomes |
| Healthcare workers performing endotracheal intubation | video guided laryngoscopy | direct laryngoscopy | 1. Disease transmission |

# Infection Control Evidence Summaries:

**Figure S4. Recommendation 3: N-95 vs surgical mask Lab confirmed influenza infection**

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**Figure S5. Recommendation 3: N-95 vs surgical mask- Lab resp infection**

****

**Figure S6. Recommendation 3: N-95 vs surgical mask- influenza-like illness**

****

**Table S6. Recommendation 3: Evidence Profile**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants (studies)** | **Relative effect (95% CI)** | **Certainty of the evidence (GRADE)** |
| **Lab-confirmed influenza** | **(4 RCTs)** | **OR 1.08 (0.84 to 1.38)** | **LOW** |
| **Lab-confirmed resp infections** | **(4 RCTs)** | **OR 0.94 (0.80 to 1.11)** | **LOW** |
| **Influenza like illness** | **(4 RCTs)** | **OR 0.76 (0.51 to 1.13)** | **LOW** |
| **Clinical resp infections** | **(3 RCTs)** | **OR 0.67 (0.44 to 1.02)** | **VERY LOW** |

# Laboratory Diagnosis and Specimens Questions:

**Table S7. PICO question: Recommendation 7.1**

|  |  |  |  |
| --- | --- | --- | --- |
| In mechanically ventilated patients with suspected COVID-19, should we recommend sending upper respiratory tract samples versus lower respiratory tract samples? | | | |
| Population | Intervention | Comparator | Outcomes |
| Mechanically ventilated adults with suspected COVID-19 infection | Upper respiratory tract sample | Lower respiratory tract sample | 1. Diagnostic accuracy 2. Patient harm 3. Infection risk to healthcare workers |

**Table S8.** **PICO question: Recommendation 7.2**

|  |  |  |  |
| --- | --- | --- | --- |
| In mechanically ventilated patients with suspected COVID-19, should we recommend sending endotracheal aspirate samples versus bronchoscopic samples? | | | |
| Population | Intervention | Comparator | Outcomes |
| Mechanically ventilated adults with suspected COVID-19 infection | Endotracheal aspirate | Bronschoscopic sample | 1. Diagnostic accuracy 2. Patient harm 3. Infection risk to healthcare workers |

# Hemodynamic support Questions:

**Table S9.** **PICO question: Recommendation 8**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we assess fluid responsiveness by dynamic or static measures? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | Dynamic parameters | Static parameters | 1. Mortality 2. Length of stay ICU 3. Duration of mechanical ventilation |

**Table S10.** **PICO question: Recommendation 9**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we use a conservative (fluid restrictive) or liberal fluid strategy? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | Conservative strategy | Liberal strategy | 1. Mortality 2. Serious adverse events 3. Ventilator-free days 4. Length of stay ICU |

**Table S11.** **PICO question: Recommendation 10**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we use intravenous crystalloids or colloids for fluid resuscitation? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | Intravenous crystalloids | Intravenous colloids | 1. Mortality 2. Serious adverse events |

**Table S12.** **PICO question: Recommendation 11**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we use buffered/balanced crystalloids or unbalanced crystalloids for fluid resuscitation? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | Balanced/buffered crystalloids | Unbalanced crystalloids | 1. Mortality 2. Serious adverse events |

**Table S13.** **PICO question: Recommendation 12**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we use hydroxyethyl starches for fluid resuscitation? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | Hydroxyethyl starches | Crystalloids | 1. Mortality 2. Renal replacement therapy 3. Blood transfusion |

**Table S14.** **PICO question: Recommendation 13**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we use gelatins for fluid resuscitation? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | Gelatins | Crystalloids | 1. Mortality |

**Table S15.** **PICO question: Recommendation 14**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we use dextrans for fluid resuscitation? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | Dextrans | Crystalloids | 1. Mortality 2. Blood transfusion |

**Table S16.** **PICO question: Recommendation 15**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we use albumin for fluid resuscitation? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | Albumin | Crystalloids | 1. Mortality 2. Renal replacement therapy 3. Blood transfusion |

**Table S17.** **PICO question: Recommendation 16**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we use norepinephrine or other vasoactive agents as first-line treatment? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | Norepinephrine | Other vasoactive agents | 1. Mortality 2. Serious adverse events |

**Table S18.** **PICO question: Recommendation 17**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we use either vasopressin or epinephrine, if norepinephrine is not available? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | Vasopressin | Epinephrine | 1. Mortality 2. Serious adverse events |

**Table S19.** **PICO question: Recommendation 18**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we use dopamine or norepinephrine? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | Dopamine | Norepinephrine | 1. Mortality 2. Arrythmias |

**Table S20.** **PICO question: Recommendation 19**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we add vasopressin as a second-line agent or should we titrate norepinephrine, if mean arterial pressure (MAP) target cannot be achieved by norepinephrine? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | Vasopressin | Norepinephrine | 1. Mortality 2. Atrial fibrillation 3. Digital ischemia |

**Table S21.** **PICO question: Recommendation 20**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock, should we titrate vasoactive agents to a MAP of 60−65 mm Hg or use higher MAP targets? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 and shock | MAP 60−65 mm Hg | MAP > 65 mm Hg | 1. Mortality 2. Arrhythmias 3. Myocardial Injury 4. Limb ischemia |

**Table S22.** **PICO question: Recommendation 21**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and shock with evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine, should we add dobutamine or increase norepinephrine dose? | | | |
| Population | Intervention | Comparator | Outcomes |
| COVID-19 and shock with evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine | Dobutamine | No dobutamine | 1. Mortality 2. Serious adverse events |

**Table S23.** **PICO question: Recommendation 22**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 and refractory shock, should we use low-dose corticosteroid therapy or not? | | | |
| Population | Intervention | Comparator | Outcomes |
| COVID-19 and refractory shock | Low-dose corticosteroids | No low-dose corticosteroids | 1. Mortality 2. Serious adverse events |

# Hemodynamic Support Evidence Summaries:

**Table S23. Recommendation 9: Evidence profile: conservative vs. liberal fluid therapy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| **All-cause Mortality** | 637 (9 RCTs) | **RR 0.87**  (0.69–1.10) | VERY LOW |
| **Serious Adverse Events** | 637 (9 RCTs) | **RR 0.91**  (0.78–1.05) | VERY LOW |

Meyhoff TS, Møller MH, Hjortrup PB, Cronhjort M, Perner A, Wetterslev J. Lower versus higher fluid volumes during initial management of sepsis - a systematic review with meta-analysis and trial sequential analysis. Chest. 2020 Jan 23. pii: S0012-3692(20)30123-9. doi: 10.1016/j.chest.2019.11.050. [Epub ahead of print] PubMed PMID: 31982391.

**Table S24. Evidence profile: Recommendation 11: buffered/balanced crystalloids vs. unbalanced crystalloids**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| **Hospital Mortality** | 19,664 (14 RCTs) | **OR 0.91**  (0.83–1.01) | HIGH |
| **Acute Kidney Injury** | 18,701 (9 RCTs) | **RR 0.91**  (0.78–1.05) | LOW |

Antequera Martín AM, Barea Mendoza JA, Muriel A, Sáez I, Chico-Fernández M, Estrada-Lorenzo JM, Plana MN. Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. Cochrane Database Syst Rev. 2019 Jul 19;7:CD012247. doi: 10.1002/14651858.CD012247.pub2. PubMed PMID: 31334842; PubMed Central PMCID: PMC6647932.

**Table S25. Evidence profile: Recommendation 12: crystalloids vs. hydroxyethyl starches**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| **All-cause Mortality (end of follow-up)** | 11,177 (24 RCTs) | **RR 0.97**  (0.86–1.09) | MODERATE |
| **All-cause Mortality (within 90 days)** | 10,415  (15 RCTs) | **RR 1.01**  (0.90–1.14) | MODERATE |
| **All-cause Mortality (within 30 days)** | 10,135  (11 RCTs) | **RR 0.99**  (0.90–1.09) | MODERATE |
| **Renal Replacement Therapy** | 8,527 (9 RCTs) | **RR 1.30**  (1.14–1.48) | MODERATE |
| **Blood transfusion** | 1,917  (8 RCTs) | **RR 1.19**  (1.02–1.39) | MODERATE |

Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018 Aug 3;8:CD000567. doi: 10.1002/14651858.CD000567.pub7. PubMed PMID: 30073665; PubMed Central PMCID: PMC6513027.

**Table S26. Evidence profile: Recommendation 13: crystalloids vs. gelatins**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| **All-cause Mortality (end of follow-up)** | 1,698 (6 RCTs) | **RR 0.89**  (0.74–1.08) | LOW |
| **All-cause Mortality (within 90 days)** | 1,388  (1 RCT) | **RR 0.89**  (0.73–1.09) | LOW |
| **All-cause Mortality (within 30 days)** | 1,388  (1 RCT) | **RR 0.92**  (0.74–1.16) | LOW |

Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018 Aug 3;8:CD000567. doi: 10.1002/14651858.CD000567.pub7. PubMed PMID: 30073665; PubMed Central PMCID: PMC6513027.

**Table S27. Evidence profile: Recommendation 14 crystalloids vs. dextrans**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| **All-cause Mortality (end of follow-up)** | 4,736 (19 RCTs) | **RR 0.99**  (0.88–1.11) | MODERATE |
| **All-cause Mortality (within 90 days)** | 3,353  (10 RCT) | **RR 0.99**  (0.87–1.12) | MODERATE |
| **Blood transfusion** | 1,272  (3 RCTs) | **RR 0.92**  (0.7–1.10) | VERY LOW |

Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018 Aug 3;8:CD000567. doi: 10.1002/14651858.CD000567.pub7. PubMed PMID: 30073665; PubMed Central PMCID: PMC6513027.

**Table S28. Evidence profile: Recommendation 15 crystalloids vs. albumin**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| **All-cause Mortality (end of follow-up)** | 13,047 (20 RCTs) | **RR 0.98**  (0.92–1.06) | MODERATE |
| **All-cause Mortality (within 90 days)** | 12,492  (10 RCTs) | **RR 0.98**  (0.92–1.04) | MODERATE |
| **All-cause Mortality (within 30 days)** | 12,506  (10 RCTs) | **RR 0.99**  (0.93–1.06) | MODERATE |
| **Renal Replacement Therapy** | 290 (2 RCTs) | **RR 1.11**  (0.96–1.27) | VERY LOW |
| **Blood transfusion** | 1,917  (3 RCTs) | **RR 1.31**  (0.95–1.80) | VERY LOW |

Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018 Aug 3;8:CD000567. doi: 10.1002/14651858.CD000567.pub7. PubMed PMID: 30073665; PubMed Central PMCID: PMC6513027.

**Table S29. Evidence profile: Recommendation 18 norepinephrine vs. dopamine**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| **All-cause Mortality (end of follow-up)** | 1,400 (6 RCTs) | **RR 1.07**  (0.99–1.16) | HIGH |
| **Arrhythmias** | 1,931  (2 RCTs) | **RR 2.34**  (1.46–3.78) | HIGH |

Gamper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M, Herkner H. Vasopressors for hypotensive shock. Cochrane Database Syst Rev. 2016 Feb 15;2:CD003709. doi: 10.1002/14651858.CD003709.pub4. Review. PubMed PMID: 26878401; PubMed Central PMCID: PMC6516856.

**Table S30. Evidence profile: Recommendation 19 vasopressin add-on vs. norepinephrine**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| **All-cause Mortality (end of follow-up)** | 3,430 (18 RCTs) | **RR 0.91**  (0.85–0.99) | LOW |
| **Atrial Fibrillation** | 1,358  (13 RCT) | **RR 0.77**  (0.67–0.88) | HIGH |
| **Digital Ischemia** | 2,489  (10 RCTs) | **RR 2.56**  (1.24–5.25) | MODERATE |

Honarmand K, Um KJ, Belley-Côté EP, Alhazzani W, Farley C, Fernando SM, Fiest K, Grey D, Hajdini E, Herridge M, Hrymak C, Møller MH, Kanji S, Lamontagne F, Lauzier F, Mehta S, Paunovic B, Singal R, Tsang JL, Wynne C, Rochwerg B. Canadian Critical Care Society clinical practice guideline: The use of vasopressin and vasopressin analogues in critically ill adults with distributive shock. Can J Anaesth. 2020 Mar;67(3):369-376. doi: 10.1007/s12630-019-01546-x. Epub 2019 Dec 3. PubMed PMID: 31797234.

**Table S31. Evidence profile: Recommendation 20 higher vs. lower MAP targets**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| **28-day Mortality** | 894 (2 RCTs) | **OR 1.15** (0.87 to 1.52) | LOW |
| **90-day Mortality** | 894 (2 RCTs) | **OR 1.08** (0.84 to 1.44) | LOW |
| **Supraventricular Arrhythmia** | 894 (2 RCTs) | **OR 2.50**  (1.35–4.77) | MODERATE |
| **Myocardial Injury** | 894 (2 RCTs) | **OR 1.47**  (0.64–3.56) | LOW |
| **Limb Ischemia** | 894 (2 RCTs) | **OR** **0.92**  (0.36–2.10) | LOW |

**Table S32. Evidence profile: Recommendation 22 corticosteroids vs. no corticosteroids in shock**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| **Short-term Mortality (<90 days)** | 7297 (22 RCTs) | **RR 0.96**  (0.91–1.02) | HIGH |
| **Long-term Mortality (>90 days)** | 5667  (5 RCTs) | **RR 0.96**  (0.90–1.02) | MODERATE |
| **Serious Adverse Events** | 5908  (10 RCTs) | **RR 0.98**  (0.90–1.08) | LOW |

# Ventilation Questions:

**Table S33. PICO question: Recommendation 23-24**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 infection and respiratory failure, what oxygenation targets should we recommend? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 infection and acute respiratory failure | Conservative oxygenation targets | Liberal oxygenation targets | 1. Mortality |

**Table S34. PICO question: Recommendation 25**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 infection and acute respiratory failure, should we recommend high flow nasal cannula (HFNC) versus conventional oxygen? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 infection and acute respiratory failure | HFNC | Conventional oxygen | 1. Mortality 2. Invasive MV 3. Patient comfort |

**Table S35.** **PICO question: Recommendation 26**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 infection and acute respiratory failure, should we recommend non-invasive positive pressure ventilation (NIPPV) versus high flow nasal cannula (HFNO)? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 infection and acute respiratory failure | NIPPV | HFNC | 1. Mortality 2. Invasive MV 3. Patient comfort |

**Table S36.** **PICO question: Recommendation 30-31**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 infection and acute respiratory failure, should we recommend ventilation using protective lung ventilation versus higher tidal volume? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 infection and acute respiratory failure | Low tidal volume (protective lung ventilation) | Higher tidal volume | 1. Mortality 2. Barotrauma |

**Table S37.** **PICO question: Recommendation 32**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 infection and moderate to severe ARDS, should we recommend ventilation using high PEEP strategy versus low PEEP strategy? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 infection and moderate to severe ARDS | High PEEP strategy | Low PEEP strategy | 1. Mortality 2. Barotrauma |

**Table S38.** **PICO question: Recommendation 34**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 infection and severe ARDS, should we recommend prone ventilation versus no proning? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 infection and severe ARDS | Prone ventilation | No prone ventilation | 1. Mortality 2. Adverse events |

**Table S39.** **PICO question: Recommendation 35**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 infection and moderate to severe ARDS, should we recommend a continuous infusion of neuromuscular blocking agent (NMBA) versus as needed NMBA boluses (no continuous infusion)? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 infection and moderate to severe ARDS | Continues NMBA infusion | As needed NMBA boluses | 1. Mortality 2. Barotrauma 3. ICUAW |

**Table S40.** **PICO question: Recommendations 36-37**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 infection ARDS, and hypoxia despite optimizing ventilation, should we recommend using inhaled pulmonary vasodilators (Nitric oxide) versus not using it? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 infection ARDS, and hypoxia despite optimizing ventilation | Inhaled pulmonary vasodilators (Nitric oxide) | Usual care | 1. Mortality 2. Renal failure |

**Table S41.** **PICO question: Recommendations 38-39**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 infection ARDS, and hypoxia despite optimizing ventilation, should we recommend using recruitment maneuvers versus no recruitment maneuvers? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 infection ARDS, and hypoxia despite optimizing ventilation | recruitment maneuvers | No recruitment maneuvers | 1. Mortality 2. Oxygenation 3. Hemodynamic compromise |

**Table S42.** **PICO question: Recommendations 40**

|  |  |  |  |
| --- | --- | --- | --- |
| In adults with COVID-19 infection ARDS and hypoxia despite optimizing ventilation and rescue therapies, should we recommend using ECMO? | | | |
| Population | Intervention | Comparator | Outcomes |
| Adults with COVID-19 infection ARDS, and hypoxia despite optimizing ventilation and rescue therapies | V-V ECMO | No ECMO | 1. Mortality 2. Renal failure |

# Ventilation Evidence Summaries:

**Table S43. Evidence profile: Recommendation 32 high PEEP vs. lower PEEP in ARDS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| **Hospital Mortality** –  With improved oxygenation to PEEP | 2,031 (6 RCTs) | **RR 0.87** (0.78 to 0.97) | MODERATE |
| **Hospital Mortality** –  Without improved oxygenation to PEEP | 1,557 (2 RCTs) | **RR 1.08** (0.98 to 1.18) | MODERATE |
| **Barotrauma** –  With improved oxygenation to PEEP | 2,089 (7 RCTs) | **RR 0.80** (0.48 to 1.35) | MODERATE |
| **Barotrauma** –  Without improved oxygenation to PEEP | 1,559 (2 RCTs) | **RR 2.50** (1.64 to 3.79) | MODERATE |

**Table S44. Evidence profile: Recommendation 34: prone ventilation vs. supine ventilation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| Mortality  >12 hours prone | 1,002 (5 RCTs) | **RR 0.71** (0.52 to 0.97) | MODERATE |
| Mortality  <12 hours prone | 1,135 (3 RCTs) | **RR 1.04** (0.89 to 1.21) | MODERATE |
| Mortality –  Moderate to severe ARDS | 1,002 (5 RCTs) | **RR 0.71** (0.52 to 0.97) | MODERATE |
| Mortality - All ARDS | 1,135 (3 RCTs) | **RR 1.04** (0.89 to 1.21) | MODERATE |
| Accidental CVC Removal | 635 (2 RCTs) | **RR 1.72** (0.43 to 6.84) | VERY LOW |
| Pressure Sores | 1,087 (3 RCTs) | **RR 1.22** (1.06 to 1.41) | HIGH |
| Airway Complications –  Unplanned extubation | 2,067 (6 RCTs) | **RR 1.14** (0.78 to 1.67) | LOW |
| Airway Complications –  ETT Obstruction | 1,594 (3 RCTs) | **RR 1.76** (1.24 to 2.50) | MODERATE |

**Table S45. Evidence profile: Recommendation 35: continues NMBA infusion vs. intermittent as needed NMBA in ARDS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| **Hospital Mortality** -  (deep sedation in control arm) | 431 (3 RCTs) | **RR 0.72** (0.58 to 0.91) | LOW |
| **Hospital mortality** -  (light sedation in control arm) | 1,006 (1 RCT) | **RR 0.99** (0.86 to 1.15) | MODERATE |
| **Barotrauma** | 1,437 (4 RCTs) | **RR 0.55** (0.35 to 0.85) | MODERATE |
| **ICUAW** | 885 (4 RCTs) | **RR 1.16** (0.98 to 1.37) | MODERATE |

**Table S46. Evidence profile: Recommendations 38-39: RM vs. no RM in ARDS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **№ of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| Hospital Mortality | 2,544 (8 RCTs) | **RR 0.90** (0.78 to 1.04) | MODERATE |
| Hospital Mortality –  Traditional Recruitment Maneuver | 1,345 (4 RCTs) | **RR 0.85** (0.75 to 0.97) | MODERATE |
| Hospital Mortality –  Incremental PEEP Recruitment | 1,199 (4 RCTs) | **RR 1.06** (0.97 to 1.17) | MODERATE |
| Mortality at 28-days –  Traditional Recruitment Maneuver | 1,346 (4 RCTs) | **RR 0.79** (0.64 to 0.96) | MODERATE |
| Mortality at 28-days –  Incremental PEEP Recruitment | 1,200 (4 RCTs) | **RR 1.12** (1.00 to 1.25) | MODERATE |
| Barotrauma | 1,407 (5 RCTs) | **RR 0.79** (0.46 to 1.37) | LOW |

**Table S47. Evidence Profile: Recommendation 40: VV ECMO versus no ECMO in ARDS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **No. of participants** **(studies)** | **Relative effect** **(95% CI)** | **Certainty of the evidence** |
| 60-day Mortality | 429 (2 RCTs) | **RR 0.73** (0.57 to 0.92) | LOW |
| Bleeding - Massive transfusion | 249 (1 RCT) | **RR 3.02** (0.32 to 28.68) | LOW |
| Bleeding - leading to transfusion | 249 (1 RCT) | **RR 1.64** (1.17 to 2.31) | LOW |

# Therapy group Questions:

**Table S48.** **PICO question: Recommendation 41**

|  |  |  |  |
| --- | --- | --- | --- |
| In mechanically ventilated adults with COVID-19 and respiratory failure (**without ARDS**), should we recommend using systemic corticosteroids, compared to no corticosteroids? | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Mechanically ventilated patients with COVID-19 and respiratory failure  (Not ARDS) | Systemic corticosteroids | No corticosteroids | 1. Mortality 2. Organ failure 3. Infection 4. Neuromuscular Weakness 5. GI Hemorrhage 6. Hyperglycemia 7. Viral load |

**Table S49.** **PICO question: Recommendation 42**

|  |  |  |  |
| --- | --- | --- | --- |
| In mechanically ventilated adults with COVID-19 and **ARDS**, should we recommend using systemic corticosteroids, compared to no corticosteroids? | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Mechanically ventilated patients with COVID-19 **and ARDS** | Systemic corticosteroids | No corticosteroids | 1. Mortality 2. Organ failure 3. Infection 4. Neuromuscular Weakness 5. GI Hemorrhage 6. Hyperglycemia 7. Viral load |

**Table S50. PICO question: Recommendation 43**

|  |  |  |  |
| --- | --- | --- | --- |
| In mechanically ventilated adults with COVID-19 and respiratory failure, should we recommend using empiric antimicrobials (antibacterial), versus no antimicrobials? | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Mechanically ventilated patients with COVID-19 and respiratory failure | Empiric antimicrobials (antibacterial) | No antimicrobials | 1. Mortality 2. Adverse events |

**Table S51. PICO question: Recommendation 44**

|  |  |  |  |
| --- | --- | --- | --- |
| In critically ill adults with COVID-19, should we recommend fever management, versus no intervention? | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill adults with COVID-19 with fever | Fever management | No intervention | 1. Mortality 2. Adverse events 3. Patient comfort 4. Shock |

**Table S53. PICO question: Recommendation 45**

|  |  |  |  |
| --- | --- | --- | --- |
| In mechanically ventilated adults with COVID-19, should we recommend using intravenous immunoglobulins (IVIG), versus no IVIG? | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Mechanically ventilated adults with COVID-19 | IVIG | No IVIG | 1. Mortality 2. Adverse events |

**Table S54. PICO question: Recommendation 46**

|  |  |  |  |
| --- | --- | --- | --- |
| In mechanically ventilated adults with COVID-19 infection, should we recommend using convalescent plasma, versus no convalescent plasma? | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Mechanically ventilated patients with COVID-19 | Convalescent plasma | No convalescent plasma | 1. Mortality 2. Adverse events |

**Table S55. PICO question: Recommendation 47**

|  |  |  |  |
| --- | --- | --- | --- |
| In critically ill adults with COVID-19, should we recommend using antivirals, versus no antiviral agents,? | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill adults with COVID-19 | Antivirals | No antivirals | 1. Mortality 2. Adverse events |

**Table S56. PICO question: Recommendation 48**

|  |  |  |  |
| --- | --- | --- | --- |
| In mechanically ventilated adults with COVID-19, should we recommend using interferon, versus no interferon therapy? | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Mechanically ventilated adults with COVID-19 | Interferon | No interferon | 1. Mortality 2. Adverse events |

**Table S57. PICO question: Recommendation 49**

|  |  |  |  |
| --- | --- | --- | --- |
| Should we recommend using chloroquine, versus no antiviral agents, in critically ill adults with COVID-19 infection? | | | |
| Population | Intervention | Comparator | Outcome(s) |
| critically ill adults with COVID-19 | Chloroquine | No Agent | 1. Mortality 2. Adverse events |

# Therapy Evidence Summaries:

**Figure S7. Mortality outcome: recommendation 41: observational studies on viral pneumonia**

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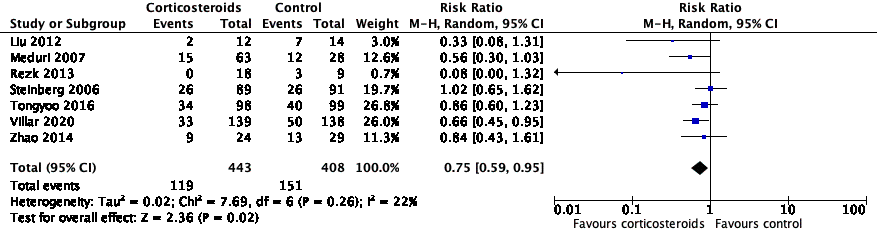
**Table S58. Evidence Profile: Recommendation 41: Corticosteroid vs. No corticosteroid in COVID-19 without ARDS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **№ of participants (studies)** | **Relative effect (95% CI)** | **Certainty of the evidence (GRADE)** |
|
| Mortality (indirect observational studies influenza) | (8 observational studies) | **OR 2.76** (2.06 to 3.69) | ⨁◯◯◯ VERY LOW |
|
| Mortality (indirect observational studies coronaviruses) | (8 observational studies) | **OR 0.83** (0.32 to 2.17) | ⨁◯◯◯ VERY LOW |
|

**Figure S8. Mortality outcome: recommendation 41: observational studies on viral ARDS**

****

**Figure S9. Mortality outcome: recommendation 41: RCTs on ARDS (not specific to viral ARDS)**

****

**Table S59. Evidence Profile: Recommendation 42: Corticosteroid vs. No corticosteroid in COVID-19 with ARDS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **№ of participants (studies)** | **Relative effect (95% CI)** | **Certainty of the evidence (GRADE)** |
| Mortality (Indirect evidence from ARDS RCTs) | (7 RCTs) | **RR 0.75** (0.59 to 0.95) | LOW |
| Mortality (Indirect evidence from influenza ARDS observational studies) | (5 observational studies) | **OR 1.40** (0.76 to 2.57) | VERY LOW |
| Mortality (Direct evidence from Wu et al.) | (1 observational study) | **HR 0.38** (0.20 to 0.72) | VERY LOW |

**Table S60. Evidence Profile: Recommendation 47: lopinavir/ritonavir vs. No lopinavir/ritonavir in critically ill COVID-19 patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **№ of participants (studies)** | **Relative effect (95% CI)** | **Certainty of the evidence (GRADE)** |
| 28-day Mortality | (1 RCTs) | **RD -5.8%**  (-17.3 to 5.7) | LOW |
| Time to symptoms improvement | (1 RCTs) | **MD** 1.31 days (0.95 to 1.80) | LOW |