# Appendix Table 7. EtD for viscoelastic testing recommendation

|  |  |
| --- | --- |
| Question | |
| **Should INR, platelet, fibrinogen vs. viscoelastic testing (TEG/ROTEM) be used for critically ill patients with acute or chronic liver failure to assess for bleeding and thrombosis?** | |
| **Population:** | critically ill patients with ALF or ACLF to assess for bleeding and thrombosis |
| **Intervention:** | INR, platelet, fibrinogen |
| **Comparison:** | viscoelastic testing (TEG/ROTEM) |
| **Main outcomes:** | Bleeding; Mortality; Blood product transfused (either FFP or PLT); Rate of bleeding; Rates of thrombosis; Mortality; Rates of PRBC, Plt, FFP or other blood products transfusion; Secondary Organ Failure; Hospital LOS; ICU LOS; |
| **Setting:** | Inpatient |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with viscoelastic testing (TEG/ROTEM)** | **Risk difference with INR, platelet, fibrinogen** | | Bleeding | 60 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c,d | **RR 0.33** (0.01 to 7.87) | Study population | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 1 more) | | Mortality follow up: mean 90 days | 60 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c,e | **RR 1.14** (0.47 to 2.75) | Study population | | | 267 per 1,000 | **37 more per 1,000** (141 fewer to 467 more) | | Blood product transfused (either FFP or PLT) assessed with: Number of patients who received transfused products | 60 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,f | **RR 0.18** (0.08 to 0.39) | Study population | | | 167 per 1,000 | **137 fewer per 1,000** (153 fewer to 102 fewer) |  1. De Pietri, Lesley, Bianchini, Marcello, Montalti, Roberto, De Maria, Nicola, Di Maira, Tommaso, Begliomini, Bruno, Gerunda, Giorgio Enrico, di Benedetto, Fabrizio, Garcia-Tsao, Guadalupe, Villa, Erica. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: A randomized, controlled trial. Hepatology; 2016. 2. In the study by de Pietri et al., the outcomes were measured based on the patient population receiving invasive procedures instead of examining the outcomes occurring spontaneously, as asked in this PICO. 3. Viera da Rocha et al., an observational study that followed 150 cirrhotic patients who received esophageal varices band ligation, examined a patient population direct to this PICO. This study found the following: TEG bleeding: normocoaguable: 1/16, hypocoaguable 3/55, hypercoaguable 1/21. Platelet count less than 50K: 1/18 bled and 17 of 18 did not. Platelet greater than 50 K bled in 10/132 and 122/132 did not bleed. INR greater than 1.5: 3/28 did bleed while 25/28 did not bleed. INR less than or equal to 1.5: 8/122 bled with less than 1.5 or equal to INR and 114/122 did not bleed. 4. While the trial lacked blinding, this is deemed unlikely to lead to bias in the measurement of this outcome. 5. Small sample size and CI includes values suggesting substantial benefit and values suggesting substantial harm. 6. Small sample size and CI includes values suggesting both benefit and no benefit. 7. Results are from one study with few events. |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with viscoelastic testing (TEG/ROTEM)** | **Risk difference with INR, platelet, fibrinogen** | | Bleeding | 60 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c,d | **RR 0.33** (0.01 to 7.87) | Study population | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 1 more) | | Mortality follow up: mean 90 days | 60 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c,e | **RR 1.14** (0.47 to 2.75) | Study population | | | 267 per 1,000 | **37 more per 1,000** (141 fewer to 467 more) | | Blood product transfused (either FFP or PLT) assessed with: Number of patients who received transfused products | 60 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,f | **RR 0.18** (0.08 to 0.39) | Study population | | | 167 per 1,000 | **137 fewer per 1,000** (153 fewer to 102 fewer) |  1. De Pietri, Lesley, Bianchini, Marcello, Montalti, Roberto, De Maria, Nicola, Di Maira, Tommaso, Begliomini, Bruno, Gerunda, Giorgio Enrico, di Benedetto, Fabrizio, Garcia-Tsao, Guadalupe, Villa, Erica. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: A randomized, controlled trial. Hepatology; 2016. 2. In the study by de Pietri et al., the outcomes were measured based on the patient population receiving invasive procedures instead of examining the outcomes occurring spontaneously, as asked in this PICO. 3. Viera da Rocha et al., an observational study that followed 150 cirrhotic patients who received esophageal varices band ligation, examined a patient population direct to this PICO. This study found the following: TEG bleeding: normocoaguable: 1/16, hypocoaguable 3/55, hypercoaguable 1/21. Platelet count less than 50K: 1/18 bled and 17 of 18 did not. Platelet greater than 50 K bled in 10/132 and 122/132 did not bleed. INR greater than 1.5: 3/28 did bleed while 25/28 did not bleed. INR less than or equal to 1.5: 8/122 bled with less than 1.5 or equal to INR and 114/122 did not bleed. 4. While the trial lacked blinding, this is deemed unlikely to lead to bias in the measurement of this outcome. 5. Small sample size and CI includes values suggesting substantial benefit and values suggesting substantial harm. 6. Small sample size and CI includes values suggesting both benefit and no benefit. 7. Results are from one study with few events. |  |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies |  |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability |  | Main outcomes are mortality, bleeding, and blood products transfused. Probably no important variability between patients. |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know |  | TEG device is required; however, blood product expenses are saved. FFP is probably more expensive than the TEG chemicals required. |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

# Appendix Table 8. EtD for transfusion threshold recommendation

|  |  |
| --- | --- |
| Question | |
| **Should hemoglobin of seven vs. other levels be used for transfusion in critically ill patients with chronic liver failure, who are not actively bleeding?** | |
| **Population:** | transfusion in critically ill patients with ALF or ACLF, who are not actively bleeding |
| **Intervention:** | hemoglobin of seven |
| **Comparison:** | other levels |
| **Main outcomes:** | Transfusion Complications (includes fever, transfusion-related circulatory overload, and allergic reactions); All-cause mortality; Red-cell transfusions; Units of red-cells transfused; Secondary infections; Adverse events (transfusion reactions, cardiac complications, pulmonary complications, acute kidney injury, stroke, or bacterial infections); Secondary organ failure; Hospital LOS; ICU LOS; Acute on chronic liver failure; |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with other levels** | **Risk difference with hemoglobin of seven** | | Transfusion Complications (includes fever, transfusion-related circulatory overload, and allergic reactions) | 889 (1 RCT)1 | ⨁⨁⨁◯ MODERATEa,b | **RR 0.36** (0.20 to 0.66) | Study population | | | 85 per 1,000 | **55 fewer per 1,000** (68 fewer to 29 fewer) | | All-cause mortality follow up: 6 weeks | 277 (1 RCT)1 | ⨁⨁⨁◯ MODERATEa,c,d | **HR 0.57** (0.30 to 1.08) | Study population | | | 181 per 1,000 | **73 fewer per 1,000** (123 fewer to 13 more) | | Red-cell transfusions | 889 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,e,f | **RR 0.57** (0.52 to 0.63) | Study population | | | 863 per 1,000 | **371 fewer per 1,000** (414 fewer to 319 fewer) | | Units of red-cells transfused | 889 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,e | - | The mean units of red-cells transfused was **0** units | MD **2.2 units lower** (2.61 lower to 1.76 lower) | | Secondary infections | 889 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c | **RR 1.14** (0.92 to 1.40) | Study population | | | 268 per 1,000 | **38 more per 1,000** (21 fewer to 107 more) | | Adverse events (transfusion reactions, cardiac complications, pulmonary complications, acute kidney injury, stroke, or bacterial infections) | 889 (1 RCT)1 | ⨁⨁⨁◯ MODERATEa,b | **RR 0.84** (0.72 to 0.97) | Study population | | | 481 per 1,000 | **77 fewer per 1,000** (135 fewer to 14 fewer) |  1. Villanueva, Candid, Colomo, Alan, Bosch, Alba, Concepcion, Mar, Hernandez-Gea, Virginia, Aracil, Carles, Graupera, Isabel, Poca, Maria, Alvarez-Urturi, Cristina, Gordillo, Jordi, Guarner-Argente, Carlos, Santalo, Miquel, Muniz, Eduardo, Guarner, Carlos. Transfusion strategies for acute upper gastrointestinal bleeding. New England Journal of Medicine; 2013. 2. While the trial is unclear in regards to blinding, this is deemed unlikely to lead to bias in the measurement of this outcome. 3. Serious indirectness as the outcomes reported are for both patients with and without cirrhosis and the data does not report outcomes specifically for the population this PICO addresses. 4. Serious imprecision due to small sample size/event rate and CI includes values suggesting both benefit and no benefit. 5. Outcome reported on subgroup of cirrhotic patients. 6. In the restrictive-strategy group, 39 patients without signs or symptoms, massive bleeding, or surgery received a transfusion when the hemoglobin level was higher than 7 g per deciliter. In the liberal-strategy group, 15 patients with a hemoglobin level lower than 9 g per deciliter did not receive a transfusion. 7. There is a lack of reported outcomes stratified per severity of liver disease (CPC class a vs b vs c vs liver failure) allowing for a heterogeneous population and our PICO is addressing critically ill patients. Additionally, other levels of hemoglobin could not be studied as 7 vs 9 was studied, but we don't know the optimal transfusion threshold. |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with other levels** | **Risk difference with hemoglobin of seven** | | Transfusion Complications (includes fever, transfusion-related circulatory overload, and allergic reactions) | 889 (1 RCT)1 | ⨁⨁⨁◯ MODERATEa,b | **RR 0.36** (0.20 to 0.66) | Study population | | | 85 per 1,000 | **55 fewer per 1,000** (68 fewer to 29 fewer) | | All-cause mortality follow up: 6 weeks | 277 (1 RCT)1 | ⨁⨁⨁◯ MODERATEa,c,d | **RR 0.59** (0.32 to 1.07) | Study population | | | 181 per 1,000 | **73 fewer per 1,000** (123 fewer to 13 more) | | Red-cell transfusions | 889 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,e,f | **RR 0.57** (0.52 to 0.63) | Study population | | | 863 per 1,000 | **371 fewer per 1,000** (414 fewer to 319 fewer) | | Units of red-cells transfused | 889 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,e | - | The mean units of red-cells transfused was **0** units | MD **2.2 units lower** (2.61 lower to 1.76 lower) | | Secondary infections | 889 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c | **RR 1.14** (0.92 to 1.40) | Study population | | | 268 per 1,000 | **38 more per 1,000** (21 fewer to 107 more) | | Adverse events (transfusion reactions, cardiac complications, pulmonary complications, acute kidney injury, stroke, or bacterial infections) | 889 (1 RCT)1 | ⨁⨁⨁◯ MODERATEa,b | **RR 0.84** (0.72 to 0.97) | Study population | | | 481 per 1,000 | **77 fewer per 1,000** (135 fewer to 14 fewer) |  1. Villanueva, Candid, Colomo, Alan, Bosch, Alba, Concepcion, Mar, Hernandez-Gea, Virginia, Aracil, Carles, Graupera, Isabel, Poca, Maria, Alvarez-Urturi, Cristina, Gordillo, Jordi, Guarner-Argente, Carlos, Santalo, Miquel, Muniz, Eduardo, Guarner, Carlos. Transfusion strategies for acute upper gastrointestinal bleeding. New England Journal of Medicine; 2013. 2. While the trial is unclear in regards to blinding, this is deemed unlikely to lead to bias in the measurement of this outcome. 3. Serious indirectness as the outcomes reported are for both patients with and without cirrhosis and the data does not report outcomes specifically for the population this PICO addresses. 4. Serious imprecision due to small sample size/event rate and CI includes values suggesting both benefit and no benefit. 5. Outcome reported on subgroup of cirrhotic patients. 6. In the restrictive-strategy group, 39 patients without signs or symptoms, massive bleeding, or surgery received a transfusion when the hemoglobin level was higher than 7 g per deciliter. In the liberal-strategy group, 15 patients with a hemoglobin level lower than 9 g per deciliter did not receive a transfusion. 7. There is a lack of reported outcomes stratified per severity of liver disease (CPC class a vs b vs c vs liver failure) allowing for a heterogeneous population and our PICO is addressing critically ill patients. Additionally, other levels of hemoglobin could not be studied as 7 vs 9 was studied, but we don't know the optimal transfusion threshold. |  |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies |  |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability |  |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Large savings ○ Varies ○ Don't know |  | Save blood products and the same number of tests for patients. |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 |  | Cost of the blood bank, as well as reduced mortality. Faster recovery, shorter hospital stays. |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know |  | If someone else needed blood, the intervention would increase the availability of products in the blood bank. |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  | Commonly conducted practice in the hospital to use a transfusion trigger of 7 g/dcl. |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  | Commonly conducted practice in the hospital to use a transfusion trigger of 7 g/dcl. |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | **Strong recommendation for the intervention** |
| ○ | ○ | ○ | ○ | **●** |

# Appendix Table 9. EtD for pharmacologic treatment of VTE recommendation

|  |  |
| --- | --- |
| Question | |
| **Should low molecular weight heparin (LMWH) or coumadin vs. conservative management be used for venous thromboembolism treatment in critically ill patients with acute or chronic liver failure?** | |
| **Population:** | venous thromboembolism treatment in critically ill patients with ALF or ACLF |
| **Intervention:** | low molecular weight heparin (LMWH) or coumadin |
| **Comparison:** | conservative management |
| **Main outcomes:** | Complete or partial recanalization; Major bleed (Variceal bleed); Heparin-induced thrombocytopenia; Mortality; Extension of thrombosis/complications of thrombosis; Rates of blood product transfusion; Secondary infections; Hospital LOS; ICU LOS; Acute on chronic liver failure; Requirement of transplant; |
| **Setting:** | Inpatient |
| **Perspective:** |  |
| **Background:** |  |
| **Conflict of interest:** |  |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with conservative management** | **Risk difference with low molecular weight heparin (LMWH) or coumadin** | | Complete or partial recanalization | 121 (4 observational studies)1,2,3,a | ⨁⨁◯◯ LOW | **RR 3.82** (1.86 to 7.85) | Study population | | | 128 per 1,000 | **360 more per 1,000** (110 more to 874 more) | | Major bleed (Variceal bleed) | 66 (1 observational study)1 | ⨁◯◯◯ VERY LOWb,c | **RR 0.20** (0.02 to 1.62) | Study population | | | 152 per 1,000 | **121 fewer per 1,000** (148 fewer to 94 more) | | Heparin-induced thrombocytopenia | 54 (1 observational study)1 | ⨁◯◯◯ VERY LOWc | **RR 1.94** (0.08 to 45.54) | Study population | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |  1. Senzolo, Marco, M Sartori, Teresa, Rossetto, Valeria, Burra, Patrizia, Cillo, Umberto, Boccagni, Patrizia, Gasparini, Daniele, Miotto, Diego, Simioni, Paolo, Tsochatzis, Emmanuel, A Burroughs, Kenneth. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. Liver International; 2012. 2. Francoz, C., Belghiti, J., Vilgrain, V., Sommacale, D., Paradis, V., Condat, B., Denninger, M. H., Sauvanet, A., Valla, D., Durand, F.. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut; 2005. 3. Chen, Hui, Liu, Lei, Qi, Xingshun, He, Chuangye, Wu, Feifei, Fan, Daiming, Han, Guohong. Efficacy and safety of anticoagulation in more advanced portal vein thrombosis in patients with liver cirrhosis. European journal of gastroenterology & hepatology; 2016. 4. Senzolo 2012 reported on two separate populations: complete and partial recanalization. 5. All variceal bleeds, probably not indirect to major bleed. 6. 95% CI includes the possibility of reduced harms or increased harms due to major bleeding. |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with conservative management** | **Risk difference with low molecular weight heparin (LMWH) or coumadin** | | Complete or partial recanalization | 121 (4 observational studies)1,2,3,a | ⨁⨁◯◯ LOW | **RR 3.82** (1.86 to 7.85) | Study population | | | 128 per 1,000 | **360 more per 1,000** (110 more to 874 more) | | Major bleed (Variceal bleed) | 66 (1 observational study)1 | ⨁◯◯◯ VERY LOWb,c | **RR 0.20** (0.02 to 1.62) | Study population | | | 152 per 1,000 | **121 fewer per 1,000** (148 fewer to 94 more) | | Heparin-induced thrombocytopenia | 54 (1 observational study)1 | ⨁◯◯◯ VERY LOWc | **RR 1.94** (0.08 to 45.54) | Study population | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 0 fewer) |  1. Senzolo, Marco, M Sartori, Teresa, Rossetto, Valeria, Burra, Patrizia, Cillo, Umberto, Boccagni, Patrizia, Gasparini, Daniele, Miotto, Diego, Simioni, Paolo, Tsochatzis, Emmanuel, A Burroughs, Kenneth. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. Liver International; 2012. 2. Francoz, C., Belghiti, J., Vilgrain, V., Sommacale, D., Paradis, V., Condat, B., Denninger, M. H., Sauvanet, A., Valla, D., Durand, F.. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut; 2005. 3. Chen, Hui, Liu, Lei, Qi, Xingshun, He, Chuangye, Wu, Feifei, Fan, Daiming, Han, Guohong. Efficacy and safety of anticoagulation in more advanced portal vein thrombosis in patients with liver cirrhosis. European journal of gastroenterology & hepatology; 2016. 4. Senzolo 2012 reported on two separate populations: complete and partial recanalization. 5. All variceal bleeds, probably not indirect to major bleed. 6. 95% CI includes the possibility of reduced harms or increased harms due to major bleeding. |  |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Very low ○ Low ○ Moderate ○ High ○ No included studies |  |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability |  |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 |  | Patients receive a benefit from heparin; however, there is some harm from HIT. |
| Resources required How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know |  | Cost of blood thinners added to standard of care. |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 |  | Patients with PVT are more difficult to technically transplant. |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know |  | Both interventions can be from home; however, patients with PVT are more likely to have a variceal bleed and could be ineligible for a liver transplant. |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | LMWH is subcutaneous but warfarin is oral - preference of the patient. |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  | Coagulation monitoring is needed for patients. |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

# Appendix Table 10. EtD for pharmacologic vs. mechanical VTE prophylaxis recommendation

|  |  |
| --- | --- |
| Question | |
| **Should pharmacological prophylaxis (LMWH/UFH) vs. mechanical prophylaxis (SCD) be used for venous thromboembolism prophylaxis in critically ill patients with acute or chronic liver failure ?** | |
| **Population:** | venous thromboembolism prophylaxis in critically ill patients with ALF or ACLF |
| **Intervention:** | pharmacological prophylaxis (LMWH/UFH) |
| **Comparison:** | mechanical prophylaxis (SCD) |
| **Main outcomes:** | Mortality; Mortality (obs); Bleeding; Bleeding (obs); Portal vein thrombosis; Venous thromboembolism (obs); IVC filter rates; Duration of mechanical ventilation; Rates of PRBC use; Rates of platatlet, FFP and cryoprecipitate use; ICU LOS; Hospital LOS; |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  | Intervention is LMWH NOT mechanical prophylaxis. |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with mechanical prophylaxis (SCD)** | **Risk difference with pharmacological prophylaxis (LMWH/UFH)** | | Mortality follow up: range 58+/-37 weeks to 89+/-57 weeks | 70 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c | **RR 0.65** (0.31 to 1.37) | Study population | | | 361 per 1,000 | **126 fewer per 1,000** (249 fewer to 134 more) | | Mortality (obs) | 203 (1 observational study)2 | ⨁◯◯◯ VERY LOWb,c,d,e,f | **RR 0.29** (0.07 to 1.17) | Study population | | | 143 per 1,000 | **101 fewer per 1,000** (133 fewer to 24 more) | | Bleeding follow up: range 58+/-37 weeks to 89+/-57 weeks | 70 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c | **RR 2.12** (0.20 to 22.30) | Study population | | | 28 per 1,000 | **31 more per 1,000** (22 fewer to 592 more) | | Bleeding (obs) | 203 (1 observational study)2,g | ⨁◯◯◯ VERY LOWb,c,d,f,h | **RR 0.35** (0.05 to 2.69) | Study population | | | 58 per 1,000g | **38 fewer per 1,000** (56 fewer to 99 more) | | Portal vein thrombosis follow up: 2 years | 70 (1 RCT)1,i | ⨁⨁◯◯ LOWa,b,c | **RR 0.05** (0.00 to 0.83) | Study population | | | 278 per 1,000i | **264 fewer per 1,000** (278 fewer to 47 fewer) | | Venous thromboembolism (obs) | 408 (3 observational studies)2,3,4 | ⨁◯◯◯ VERY LOWc,d,j | **RR 0.47** (0.09 to 2.32) | Study population | | | 74 per 1,000 | **39 fewer per 1,000** (67 fewer to 97 more) |  1. Villa, Erica, Camma, Calogero, Marietta, Marco, Luongo, Monica, Critelli, Rosina, Colopi, Stefano, Tata, Cristina, Zecchini, Ramona, Gitto, Stefano, Petta, Salvatore, Lei, Barbara, Bernabucci, Veronica, Vukotic, Ranka, De Maria, Nicola, Schepis, Filippo, Karampatou, Aimilia, Caporali, Cristian, Simoni, Luisa, Del Buono, Mariagrazia, Zambotto, Beatrice, Turola, Elena, Fornaciari, Giovanni, Schianchi, Susanna, Ferrari, Anna, Valla, Dominique. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology; 2012. 2. Smith, Carmen B., Hurdle, April C., Kemp, Leonette O., Sands, Christophe, Twilla, Jennifer D.. Evaluation of venous thromboembolism prophylaxis in patients with chronic liver disease. Journal of Hospital Medicine (Online); 2013. 3. Aldawood, Abdulaziz, Arabi, Yaseen, Aljumah, Abdulrahman, Alsaadi, Alawi, Rishu, Asgar, Aldorzi, Hasan, Alqahtani, Saad, Alsultan, Mohammad, Felemban, Afaf. The incidence of venous thromboembolism and practice of deep venous thrombosis prophylaxis in hospitalized cirrhotic patients. Thrombosis Journal [Electronic Resource]; 2011. 4. Walsh, Kelly A, Lewis, Daniel A, Clifford, Timothy M, Hundley, Jonathan C, Gokun, Yevgeniya, Angulo, Paul, Davis, George A. Risk factors for venous thromboembolism in patients with chronic liver disease. Annals of Pharmacotherapy; 2013. 5. Serious indirectness as the comparison in this study differs from our PICO. The PICO sought to address mechanical prophylaxis versus pharmacological prophylaxis. Villa et al. compare treatment with enoxaparin to no treatment (placebo). 6. One study reported on this outcome and included a small sample size. 7. The 95% confidence interval includes both the potential for significant benefit and harm. 8. Serious risk of bias as there was no accountability of how much the intervention was utilized (SCD). 9. 5 patients who received a combination of mechanical and pharmacological prophylaxis were excluded from the analysis. 10. 30 patients received UFH, 33 received LMWH, 1 patient received fondaparinux, and the remaining 7 received a combination of the agents to total equal to or greater than 50% of their hospital stay. The fact that different anti-coagulation agents were used was not deemed serious enough to downgrade for. 11. Bleeding event occurred on treatment doses; patient was later switched to prophylactic doses. 12. 3 patients who received a combination of mechanical and pharmacological prophylaxis were excluded from the analysis. 13. Enoxaparin-treated patients developed PVT only at weeks 105, 111, and 121 after enrollment. Overall, 3 of 34 (8.8%) enoxaparin-treated patients and 10 of 36 (27.7%) controls developed PVT (P .048). 14. Although the I-squared is 50%, heterogeneity, it was deemed not serious enough to rate down for. All confidence intervals overlap. |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with mechanical prophylaxis (SCD)** | **Risk difference with pharmacological prophylaxis (LMWH/UFH)** | | Mortality follow up: range 58+/-37 weeks to 89+/-57 weeks | 70 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c | **RR 0.65** (0.31 to 1.37) | Study population | | | 361 per 1,000 | **126 fewer per 1,000** (249 fewer to 134 more) | | Mortality (obs) | 203 (1 observational study)2 | ⨁◯◯◯ VERY LOWb,c,d,e,f | **RR 0.29** (0.07 to 1.17) | Study population | | | 143 per 1,000 | **101 fewer per 1,000** (133 fewer to 24 more) | | Bleeding follow up: range 58+/-37 weeks to 89+/-57 weeks | 70 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c | **RR 2.12** (0.20 to 22.30) | Study population | | | 28 per 1,000 | **31 more per 1,000** (22 fewer to 592 more) | | Bleeding (obs) | 203 (1 observational study)2,g | ⨁◯◯◯ VERY LOWb,c,d,f,h | **RR 0.35** (0.05 to 2.69) | Study population | | | 58 per 1,000g | **38 fewer per 1,000** (56 fewer to 99 more) | | Portal vein thrombosis follow up: 2 years | 70 (1 RCT)1,i | ⨁⨁◯◯ LOWa,b,c | **RR 0.05** (0.00 to 0.83) | Study population | | | 278 per 1,000i | **264 fewer per 1,000** (278 fewer to 47 fewer) | | Venous thromboembolism (obs) | 408 (3 observational studies)2,3,4 | ⨁◯◯◯ VERY LOWc,d,j | **RR 0.47** (0.09 to 2.32) | Study population | | | 74 per 1,000 | **39 fewer per 1,000** (67 fewer to 97 more) |  1. Villa, Erica, Camma, Calogero, Marietta, Marco, Luongo, Monica, Critelli, Rosina, Colopi, Stefano, Tata, Cristina, Zecchini, Ramona, Gitto, Stefano, Petta, Salvatore, Lei, Barbara, Bernabucci, Veronica, Vukotic, Ranka, De Maria, Nicola, Schepis, Filippo, Karampatou, Aimilia, Caporali, Cristian, Simoni, Luisa, Del Buono, Mariagrazia, Zambotto, Beatrice, Turola, Elena, Fornaciari, Giovanni, Schianchi, Susanna, Ferrari, Anna, Valla, Dominique. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology; 2012. 2. Smith, Carmen B., Hurdle, April C., Kemp, Leonette O., Sands, Christophe, Twilla, Jennifer D.. Evaluation of venous thromboembolism prophylaxis in patients with chronic liver disease. Journal of Hospital Medicine (Online); 2013. 3. Aldawood, Abdulaziz, Arabi, Yaseen, Aljumah, Abdulrahman, Alsaadi, Alawi, Rishu, Asgar, Aldorzi, Hasan, Alqahtani, Saad, Alsultan, Mohammad, Felemban, Afaf. The incidence of venous thromboembolism and practice of deep venous thrombosis prophylaxis in hospitalized cirrhotic patients. Thrombosis Journal [Electronic Resource]; 2011. 4. Walsh, Kelly A, Lewis, Daniel A, Clifford, Timothy M, Hundley, Jonathan C, Gokun, Yevgeniya, Angulo, Paul, Davis, George A. Risk factors for venous thromboembolism in patients with chronic liver disease. Annals of Pharmacotherapy; 2013. 5. Serious indirectness as the comparison in this study differs from our PICO. The PICO sought to address mechanical prophylaxis versus pharmacological prophylaxis. Villa et al. compare treatment with enoxaparin to no treatment (placebo). 6. One study reported on this outcome and included a small sample size. 7. The 95% confidence interval includes both the potential for significant benefit and harm. 8. Serious risk of bias as there was no accountability of how much the intervention was utilized (SCD). 9. 5 patients who received a combination of mechanical and pharmacological prophylaxis were excluded from the analysis. 10. 30 patients received UFH, 33 received LMWH, 1 patient received fondaparinux, and the remaining 7 received a combination of the agents to total equal to or greater than 50% of their hospital stay. The fact that different anti-coagulation agents were used was not deemed serious enough to downgrade for. 11. Bleeding event occurred on treatment doses; patient was later switched to prophylactic doses. 12. 3 patients who received a combination of mechanical and pharmacological prophylaxis were excluded from the analysis. 13. Enoxaparin-treated patients developed PVT only at weeks 105, 111, and 121 after enrollment. Overall, 3 of 34 (8.8%) enoxaparin-treated patients and 10 of 36 (27.7%) controls developed PVT (P .048). 14. Although the I-squared is 50%, heterogeneity, it was deemed not serious enough to rate down for. All confidence intervals overlap. | Bleeding rates are similar. |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies |  | This is based on bleeding as a harm. |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability |  |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 |  | Probably favors pharmacological prophylaxis within the hospital setting. |
| Resources required How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know |  | SCD more expensive than pharmacological therapy. |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 |  | SCD are more expensive and outcomes are worse. |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know |  | Cost to patients. |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | Based on patients' preference. |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

# Appendix Table 11. EtD for assessment of bleeding risk recommendation

|  |  |
| --- | --- |
| Question | |
| **Should platelet count or fibrinogen level vs. viscoelastic testing (TEG/ROTEM) be used for assessment of bleeding risk in critically ill patients with acute or chronic liver failure and undergoing invasive and surgical procedures?** | |
| **Population:** | assessment of bleeding risk in critically ill patients with ALF or ACLF and undergoing invasive and surgical procedures |
| **Intervention:** | platelet count or fibrinogen level |
| **Comparison:** | viscoelastic testing (TEG/ROTEM) |
| **Main outcomes:** | Bleeding; Mortality; Blood product transfused (either FFP or PLT); ICU LOS; Hospital LOS; |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with viscoelastic testing (TEG/ROTEM)** | **Risk difference with platelet count or fibrinogen level** | | Bleeding | 60 (1 RCT)1 | ⨁⨁⨁◯ MODERATEa,b | **RR 0.33** (0.01 to 7.87) | Study population | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 1 more) | | Mortality follow up: 90 days | 60 (1 RCT)1 | ⨁⨁⨁◯ MODERATEa,c | **RR 1.14** (0.47 to 2.75) | Study population | | | 267 per 1,000 | **37 more per 1,000** (141 fewer to 467 more) | | Blood product transfused (either FFP or PLT) assessed with: Number of patients who received transfused products | 60 (1 RCT)1 | ⨁⨁⨁◯ MODERATEb | **RR 0.18** (0.08 to 0.39) | Study population | | | 167 per 1,000 | **137 fewer per 1,000** (153 fewer to 102 fewer) |  1. De Pietri, Lesley, Bianchini, Marcello, Montalti, Roberto, De Maria, Nicola, Di Maira, Tommaso, Begliomini, Bruno, Gerunda, Giorgio Enrico, di Benedetto, Fabrizio, Garcia-Tsao, Guadalupe, Villa, Erica. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: A randomized, controlled trial. Hepatology; 2016. 2. While the trial lacked blinding as it was open label, this is deemed unlikely to lead to bias in the measurement of this outcome. 3. Results are from one study with few events and small sample size 4. Small sample size and CI includes values suggesting substantial benefit and values suggesting substantial harm |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with viscoelastic testing (TEG/ROTEM)** | **Risk difference with platelet count or fibrinogen level** | | Bleeding | 60 (1 RCT)1 | ⨁⨁⨁◯ MODERATEa,b | **RR 0.33** (0.01 to 7.87) | Study population | | | 0 per 1,000 | **0 fewer per 1,000** (0 fewer to 1 more) | | Mortality follow up: 90 days | 60 (1 RCT)1 | ⨁⨁⨁◯ MODERATEa,c | **RR 1.14** (0.47 to 2.75) | Study population | | | 267 per 1,000 | **37 more per 1,000** (141 fewer to 467 more) | | Blood product transfused (either FFP or PLT) assessed with: Number of patients who received transfused products | 60 (1 RCT)1 | ⨁⨁⨁◯ MODERATEb | **RR 0.18** (0.08 to 0.39) | Study population | | | 167 per 1,000 | **137 fewer per 1,000** (153 fewer to 102 fewer) |  1. De Pietri, Lesley, Bianchini, Marcello, Montalti, Roberto, De Maria, Nicola, Di Maira, Tommaso, Begliomini, Bruno, Gerunda, Giorgio Enrico, di Benedetto, Fabrizio, Garcia-Tsao, Guadalupe, Villa, Erica. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: A randomized, controlled trial. Hepatology; 2016. 2. While the trial lacked blinding as it was open label, this is deemed unlikely to lead to bias in the measurement of this outcome. 3. Results are from one study with few events and small sample size 4. Small sample size and CI includes values suggesting substantial benefit and values suggesting substantial harm |  |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ● Moderate ○ High ○ No included studies |  |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability |  | Main outcomes are mortality, bleeding, and blood products transfused. Probably no important variability between patients. |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know |  | TEG device is required; however, blood product expenses are saved. FFP is probably more expensive than the TEG chemicals required. |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | **Strong recommendation for the intervention** |
| ○ | ○ | ○ | ○ | **●** |

# Appendix Table 12. EtD for novel agents in thrombocytopenia management recommendation

|  |  |
| --- | --- |
| Question | |
| **Should fresh frozen plasma (FFP)/ cryoprecipitate, prothrombin concentrates, Tranexamic/ Aminocaproic acid, Eltrombopag vs. avoiding the use of FFP/ prothrombin concentrates be used for achieving pre-procedure/surgery hematologic targets in critically ill patients with acute or chronic liver failure?** | |
| **Population:** | achieving pre-procedure/surgery hematologic targets in critically ill patients with ALF or ACLF |
| **Intervention:** | fresh frozen plasma (FFP)/ cryoprecipitate, prothrombin concentrates, Tranexamic/ Aminocaproic acid, Eltrombopag |
| **Comparison:** | avoiding the use of FFP/ prothrombin concentrates |
| **Main outcomes:** | Mortality; Serious adverse events (hepatic encephalopathy, mesenteric-vein thrombosis, cataracts, encephalopathy, gastroenteritis, rectal hemorrhage, sepsis); Bleeding; Adverse events leading to treatment discontinuation; Thrombotic events; Blood product use; ICU LOS; Hospital LOS; Complications of transfusions; |
| **Setting:** | Inpatient |
| **Perspective:** |  |
| **Background:** |  |
| **Conflict of interest:** |  |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with avoiding the use of FFP/ prothrombin concentrates** | **Risk difference with fresh frozen plasma (FFP)/ cryoprecipitate, prothrombin concentrates, Tranexamic/ Aminocaproic acid, Eltrombopag** | | Mortality follow up: 30 days | 292 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c,d,e | **RR 1.52** (0.26 to 8.97) | Study population | | | 14 per 1,000 | **7 more per 1,000** (10 fewer to 108 more) | | Serious adverse events (hepatic encephalopathy, mesenteric-vein thrombosis, cataracts, encephalopathy, gastroenteritis, rectal hemorrhage, sepsis) follow up: 30 days | 292 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c,d,e | **RR 1.13** (0.61 to 2.09) | Study population | | | 116 per 1,000 | **15 more per 1,000** (45 fewer to 126 more) | | Bleeding assessed with: WHO grade 1-4; patients who did not require a platelet transfusion before, during, and up to 7 days after the elective invasive procedure follow up: 7 days | 292 (1 RCT)1 | ⨁⨁⨁◯ MODERATEa,b,c,e | **RR 3.77** (2.66 to 5.34) | Study population | | | 190 per 1,000 | **528 more per 1,000** (316 more to 827 more) | | Adverse events leading to treatment discontinuation follow up: 30 days | 292 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c,d,e | **RR 1.01** (0.21 to 4.94) | Study population | | | 20 per 1,000 | **0 fewer per 1,000** (16 fewer to 80 more) | | Thrombotic events follow up: 30 days | 292 (1 RCT)1 | ⨁◯◯◯ VERY LOWa,b,c,d,e,f | **RR 3.04** (0.62 to 14.82) | Study population | | | 14 per 1,000 | **28 more per 1,000** (5 fewer to 188 more) |  1. Afdhal, Nezam H, Giannini, Edoardo G, Tayyab, Ghias, Mohsin, Aftab, Lee, Jin-Woo, Andriulli, Angelo, Jeffers, Lennox, McHutchison, John, Chen, Pei-Jer, Han, Kwang-Hyub. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. New England Journal of Medicine; 2012. 2. 2 people dropped out in each group prior to placebo/intervention administration; however, ITT analysis was conducted, therefore this most likely does not introduce considerable bias. 3. Confounding co-morbidities that can affect the outcome. Additionally, these co-morbidities are not a direct representation of the overall population this PICO addresses. 4. Eltrombopag is used vs. placebo. Increased incidence of FFP. 5. 95% CI includes both appreciable benefit and harm. 6. While funded completely by GlaxoSmithKline, no difference was found between treatment groups. 7. Serious risk of bias measurement as there is no baseline study to document lack of thrombosis or measure thrombosis progression | Evidence only reports on Eltrombopag. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with avoiding the use of FFP/ prothrombin concentrates** | **Risk difference with fresh frozen plasma (FFP)/ cryoprecipitate, prothrombin concentrates, Tranexamic/ Aminocaproic acid, Eltrombopag** | | Mortality follow up: 30 days | 292 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c,d,e | **RR 1.52** (0.26 to 8.97) | Study population | | | 14 per 1,000 | **7 more per 1,000** (10 fewer to 108 more) | | Serious adverse events (hepatic encephalopathy, mesenteric-vein thrombosis, cataracts, encephalopathy, gastroenteritis, rectal hemorrhage, sepsis) follow up: 30 days | 292 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c,d,e | **RR 1.13** (0.61 to 2.09) | Study population | | | 116 per 1,000 | **15 more per 1,000** (45 fewer to 126 more) | | Bleeding assessed with: WHO grade 1-4; patients who did not require a platelet transfusion before, during, and up to 7 days after the elective invasive procedure follow up: 7 days | 292 (1 RCT)1 | ⨁⨁⨁◯ MODERATEa,b,c,e | **RR 3.77** (2.66 to 5.34) | Study population | | | 190 per 1,000 | **528 more per 1,000** (316 more to 827 more) | | Adverse events leading to treatment discontinuation follow up: 30 days | 292 (1 RCT)1 | ⨁⨁◯◯ LOWa,b,c,d,e | **RR 1.01** (0.21 to 4.94) | Study population | | | 20 per 1,000 | **0 fewer per 1,000** (16 fewer to 80 more) | | Thrombotic events follow up: 30 days | 292 (1 RCT)1 | ⨁◯◯◯ VERY LOWa,b,c,d,e,f | **RR 3.04** (0.62 to 14.82) | Study population | | | 14 per 1,000 | **28 more per 1,000** (5 fewer to 188 more) |  1. Afdhal, Nezam H, Giannini, Edoardo G, Tayyab, Ghias, Mohsin, Aftab, Lee, Jin-Woo, Andriulli, Angelo, Jeffers, Lennox, McHutchison, John, Chen, Pei-Jer, Han, Kwang-Hyub. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. New England Journal of Medicine; 2012. 2. 2 people dropped out in each group prior to placebo/intervention administration; however, ITT analysis was conducted, therefore this most likely does not introduce considerable bias. 3. Confounding co-morbidities that can affect the outcome. Additionally, these co-morbidities are not a direct representation of the overall population this PICO addresses. 4. Eltrombopag is used vs. placebo. Increased incidence of FFP. 5. 95% CI includes both appreciable benefit and harm. 6. While funded completely by GlaxoSmithKline, no difference was found between treatment groups. 7. Serious risk of bias measurement as there is no baseline study to document lack of thrombosis or measure thrombosis progression | Based on increased bleeding risk. |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies |  |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability |  |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ● 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 |  | No desirable effects and large undesirable effects. |
| Resources required How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know |  | Eltrombopag is expensive. |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 |  | Based on long-term outcomes from undesirable consequences. |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know |  |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know |  | Eltrombopag is not on the market anymore. |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 |

# Appendix Table 13. EtD for low vs. high tidal volume ventilation recommendation

|  |  |
| --- | --- |
| Question | |
| **Should Low Tidal Volume (< 6ml/Kg) vs. Tidal Volume > 8ml/Kg be used for mechanically ventilated patients with acute or acute on chronic liver failure?** | |
| **Population:** | mechanically ventilated patients with ALF or ACLF |
| **Intervention:** | Low Tidal Volume (< 6ml/Kg) |
| **Comparison:** | Tidal Volume > 8ml/Kg |
| **Main outcomes:** | Mortality; Ventilator Free Days; Barotrauma; Transplant Free Survival; |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know | | **Outcomes** | **With Tidal Volume > 8ml/Kg** | **With Low Tidal Volume (< 6ml/Kg)** | **Difference** | **Relative effect (95% CI)** | | --- | --- | --- | --- | --- | | Mortality | 422 per 1,000 | **338 per 1,000** (279 to 414) | **84 fewer per 1,000** (143 fewer to 8 fewer) | **RR 0.80** (0.66 to 0.98) | | Ventilator Free Days | The mean ventilator Free Days was **0** days | The mean ventilator Free Days in the intervention group was 0.03 days higher (5.88 lower to 5.95 higher) | MD **0.03 days higher** (5.88 lower to 5.95 higher) | - | | Barotrauma | 107 per 1,000 | **103 per 1,000** (72 to 147) | **4 fewer per 1,000** (35 fewer to 40 more) | **RR 0.96** (0.67 to 1.37) | | Transplant Free Survival - not reported | 0 per 1,000 | **0 per 1,000** (0 to 0) | **0 fewer per 1,000** (0 fewer to 0 fewer) | - | | The panel felt that mortality magnitude was large 8-14% which trumps other outcomes |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | Walkey AJ, Goligher EC, Del Sorbo L, et al. Low Tidal Volume versus Non-Volume-Limited Strategies for Patients with Acute Respiratory Distress Syndrome. A Systematic Review and Meta- Analysis. Ann Am Thorac Soc 2017;14(Supplement\_4):S271-S279.   | **Outcomes** | **With Tidal Volume > 8ml/Kg** | **With Low Tidal Volume (< 6ml/Kg)** | **Difference** | **Relative effect (95% CI)** | | --- | --- | --- | --- | --- | | Mortality | 422 per 1,000 | **338 per 1,000** (279 to 414) | **84 fewer per 1,000** (143 fewer to 8 fewer) | **RR 0.80** (0.66 to 0.98) | | Ventilator Free Days | The mean ventilator Free Days was **0** days | The mean ventilator Free Days in the intervention group was 0.03 days higher (5.88 lower to 5.95 higher) | MD **0.03 days higher** (5.88 lower to 5.95 higher) | - | | Barotrauma | 107 per 1,000 | **103 per 1,000** (72 to 147) | **4 fewer per 1,000** (35 fewer to 40 more) | **RR 0.96** (0.67 to 1.37) | | Transplant Free Survival - not reported | 0 per 1,000 | **0 per 1,000** (0 to 0) | **0 fewer per 1,000** (0 fewer to 0 fewer) | - | | Extending sedation time to use tidal volume, but ARDSnet did not support that (potential for extending).  But VFD was not helpful as indirect evidence.  No existing evidence to support this concern, but the panel felt there is possibly a small harm (to be conservative). |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ● Moderate ○ High ○ No included studies | | **Outcomes** | **Importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Mortality | CRITICAL | ⨁⨁⨁◯ MODERATEa | | Ventilator Free Days | CRITICAL | ⨁◯◯◯ VERY LOWb,c | | Barotrauma | CRITICAL | ⨁⨁◯◯ LOWa,d | | Transplant Free Survival - not reported | CRITICAL | - |  1. We downgraded the quality of evidence by one level for indirectness of population, the population described in the meta-analysis were critically ill patients with ARDS of which minority are patients with decompensated liver disease 2. We downgraded the quality of evidence by one level for serious indirectness, the population in these trials were different from the population of interest, also the outcome was measured differently in these RCTs 3. We downgraded the quality of evidence by two levels for very serious imprecision, the CI included both extreme reduction and extreme increase in VFDs 4. We downgraded the quality of evidence by one level, the CI is wide including both significant benefit and harm | Panel members felt mortality is the most crucial outcome, and even in the context of low QoE for other less critical outcome, we decided not to penalize the over the overall QoE. |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability | No evidence (Burns et al) | Panel acted as proxies for patients and felt that majority of patients would have consistent V&P    Some patient’s pre- morbid status my affect their decision. |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know |  | Likely the intervention is less costly but can't comment on savings |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 |  | Can't make comments without CEA |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | No evidence (Jonathon to provide audits) | Easy to implement, issues with compliance but not clear why |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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** |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

|  |
| --- |
|  |

# Appendix Table 14. EtD for high vs low PEEP recommendation

|  |  |
| --- | --- |
| Question | |
| **Should High PEEP vs. low PEEP be used for patients with acute liver failure with ARDS?** | |
| **Population:** | patients with ALF or ACLF with ARDS |
| **Intervention:** | High PEEP |
| **Comparison:** | low PEEP |
| **Main outcomes:** | Mortality; Transplant free survival; Oxygenation; Worsening Intracranial Pressure (ICP); |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know | Walkey AJ, Del Sorbo L, Hodgson CL, et al. Higher PEEP versus Lower PEEP Strategies for Patients with Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc 2017;14(Supplement\_4):S297-S303.  Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 2010;303(9):865-873   | **Outcomes** | **Anticipated absolute effects\* (95% CI)** | | **Relative effect (95% CI)** | **№ of participants (studies)** | **Certainty of the evidence (GRADE)** | **Comments** | | --- | --- | --- | --- | --- | --- | --- | | **Risk with low PEEP** | **Risk with High PEEP** | | Mortality | Study population | | **RR 0.91** (0.80 to 1.03) | 2580 (6 RCTs) | ⨁⨁◯◯ LOWa,b |  | | 300 per 1,000 | **273 per 1,000** (240 to 309) | | Low | | | 450 per 1,000 | **410 per 1,000** (360 to 464) | | Transplant free survival - not reported | **-** | **-** | - | - | - |  | | Oxygenation  assessed with: PO2/FiO2 | The mean oxygenation was **0** units | MD **61.24 units higher** (45.92 higher to 76.57 higher) | - | 2458 (6 RCTs) | ⨁⨁⨁◯ MODERATEa,c |  |  1. We downgraded the quality of evidence by one level for indirectness of population 2. We downgraded the quality of evidence by one level for serious imprecision 3. Although I2>80%, we did not downgrade for inconsistency because the variability in point estimates were clinically irrelevant |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know | | **Outcomes** | **Anticipated absolute effects\* (95% CI)** | | **Relative effect (95% CI)** | **№ of participants (studies)** | **Certainty of the evidence (GRADE)** | **Comments** | | --- | --- | --- | --- | --- | --- | --- | | **Risk with low PEEP** | **Risk with High PEEP** | | Mortality | Study population | | **RR 0.91** (0.80 to 1.03) | 2580 (6 RCTs) | ⨁⨁◯◯ LOWa,b |  | | 300 per 1,000 | **273 per 1,000** (240 to 309) | | Low | | | 450 per 1,000 | **410 per 1,000** (360 to 464) | | Transplant free survival - not reported | **-** | **-** | - | - | - |  | | Oxygenation  assessed with: PO2/FiO2 | The mean oxygenation was **0** units | MD **61.24 units higher** (45.92 higher to 76.57 higher) | - | 2458 (6 RCTs) | ⨁⨁⨁◯ MODERATEa,c |  |  1. We downgraded the quality of evidence by one level for indirectness of population 2. We downgraded the quality of evidence by one level for serious imprecision 3. Although I2>80%, we did not downgrade for inconsistency because the variability in point estimates were clinically irrelevant | concerns about PEEP could potentially increase ICP (case series)  low quality evidence  uncertainty about the effect on ICP in this population    Concern about reducing CO and increasing right heart pressures and worsening liver congestion |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Very low ○ Low ○ Moderate ○ High ○ No included studies | | **Outcomes** | **Importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Mortality | CRITICAL | ⨁⨁◯◯ LOWa,b | | Transplant free survival - not reported |  | - | | Oxygenation  assessed with: PO2/FiO2 | IMPORTANT | ⨁⨁⨁◯ MODERATEa,c | | Worsening ICP |  | - |  1. We downgraded the quality of evidence by one level for indirectness of population 2. We downgraded the quality of evidence by one level for serious imprecision 3. Although I2>80%, we did not downgrade for inconsistency because the variability in point estimates were clinically irrelevant |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability | No research evidence | Quality of survivors would be different if there was a true effect on ICP |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know |  |  |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 |  |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | No research evidence in this context |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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** |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○ | **●** | ○ | ○ | ○ |

# Appendix Table 15. EtD for HFNC vs NIV recommendation

|  |  |
| --- | --- |
| Question | |
| **Should HFNC vs. NIPPV be used for hypoxic critically ill patients with acute/acute on chronic liver failure?** | |
| **Population:** | hypoxic critically ill patients with ALF or ACLF |
| **Intervention:** | HFNC |
| **Comparison:** | NIPPV |
| **Main outcomes:** | Mortality- indirect evidence from all critically ill; Need for intubation- indirect evidence; |
| **Setting:** | ICU |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know | Ni YN, Luo J, Yu H, et al. Can High-flow Nasal Cannula Reduce the Rate of Endotracheal Intubation in Adult Patients With Acute Respiratory Failure Compared With Conventional Oxygen Therapy and Noninvasive Positive Pressure Ventilation?: A Systematic Review and Meta-analysis. Chest 2017;151(4):764-775.   | **Outcomes** | **With NIPPV** | **With HFNC** | **Difference** | **Relative effect (95% CI)** | | --- | --- | --- | --- | --- | | Mortality- indirect evidence from all critically ill | 103 per 1,000 | **67 per 1,000** (37 to 119) | **35 fewer per 1,000** (65 fewer to 16 more) | **OR 0.63** (0.34 to 1.18) | | Need for intubation- indirect evidence | 230 per 1,000 | **179 per 1,000** (123 to 253) | **51 fewer per 1,000** (107 fewer to 22 more) | **OR 0.73** (0.47 to 1.13) | | adverse effects of PPV in liver failure      HFNC is better tolerated by patients |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know | | **Outcomes** | **With NIPPV** | **With HFNC** | **Difference** | **Relative effect (95% CI)** | | --- | --- | --- | --- | --- | | Mortality- indirect evidence from all critically ill | 103 per 1,000 | **67 per 1,000** (37 to 119) | **35 fewer per 1,000** (65 fewer to 16 more) | **OR 0.63** (0.34 to 1.18) | | Need for intubation- indirect evidence | 230 per 1,000 | **179 per 1,000** (123 to 253) | **51 fewer per 1,000** (107 fewer to 22 more) | **OR 0.73** (0.47 to 1.13) | | May mask the severity of underlying respiratory failure. Correct hypoxia but respiratory mechanics don't change.    The setup must be done correctly, maintenance is harder with NIV. |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies | | **Outcomes** | **Importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Mortality- indirect evidence from all critically ill | CRITICAL | ⨁⨁◯◯ LOWa,b | | Need for intubation- indirect evidence | CRITICAL | ⨁⨁◯◯ LOWb,c |  1. We downgraded the quality of evidence by one level for serious inconsistency, the I2= 67% with clear inconsistency in magnitude of benefit/harm 2. We downgraded the quality of evidence by one level for serious imprecision, the CI crossed the line of unity and included both significant benefit and trivial harm 3. We downgraded the quality of evidence by one level for serious inconsistency, the I2=62% |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability |  |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 |  | comfort on the device, patient can communicate, we put more weight on these benefits |
| Resources required How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know | No research evidence | No data available  seems that maintenance NIPPV is likely more expensive and labor intensive  we chose negligible as no data is available, but the panel felt it might result in moderate cost savings |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 |  | Panel felt it may be cost effective but good evidence is not available |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | Availability of the setup could be a potential barrier for implementation  learning curve is not steep |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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** |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

# Appendix Table 16. EtD for intra-operative RRT Recommendation

|  |  |
| --- | --- |
| Question | |
| **Should renal replacement therapy (RRT) vs. no renal replacement therapy be used for critically ill patients with chronic liver disease who are undergoing liver transplant surgery?** | |
| **Population:** | ALF or ACLF during liver transplant |
| **Intervention:** | renal replacement therapy (RRT) |
| **Comparison:** | no renal replacement therapy |
| **Main outcomes:** | Mortality; Graft Dysfunction; |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know | *See Appendix 1* |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know | *See Appendix 1* | Are these undesirable effects specific to dialysis in OR versus general dialysis?    Frequency might be low but mortality when they happen, is high.    Nurses running dialysis in OR are in unfamiliar environment prone to errors.    Overall it is an issue of doing CRRT/dialysis in the OR rather than the intervention.    Conventional dialysis for example requires running water which is not available even in modern facilities. |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Very low ○ Low ○ Moderate ○ High ○ No included studies |  |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability |  |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know | No available studies | Consensus: based on the literature we reviewed, we do not know. |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies | No available studies |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 | No available studies |  |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  | . |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  |  |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | **Conditional recommendation for either the intervention or the comparison** | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○ | ○ | **●** | ○ | ○ |

Appendices

Appendix 1

1. LaMattina JC, Kelly PJ, Hanish SI, et al. Intraoperative Continuous Veno-Venous Hemofiltration Facilitates Surgery in Liver Transplant Patients With Acute Renal Failure. Transplant Proc 2015;47(6):1901-1904.
2. Agopian VG, Dhillon A, Baber J, et al. Liver transplantation in recipients receiving renal replacement therapy: outcomes analysis and the role of intraoperative hemodialysis. Am J Transplant 2014;14(7):1638-1647.
3. Parmar A, Bigam D, Meeberg G, et al. An evaluation of intraoperative renal support during liver transplantation: a matched cohort study. Blood Purif 2011;32(3):238-248.

| **Outcomes** | **With no renal replacement therapy** | **With renal replacement therapy (RRT)** | **Difference** | **Relative effect (95% CI)** |
| --- | --- | --- | --- | --- |
| Mortality | 167 per 1,000 | **154 per 1,000** (74 to 293) | **13 fewer per 1,000** (93 fewer to 126 more) | **OR 0.91** (0.40 to 2.07) |
| Graft Dysfunction | 125 per 1,000 | **72 per 1,000** (37 to 134) | **53 fewer per 1,000** (88 fewer to 9 more) | **OR 0.54** (0.27 to 1.08) |

# Appendix Table 17. EtD for early RRT recommendation

|  |  |
| --- | --- |
| Question | |
| **Should early renal replacement therapy (RRT) vs. late RRT be used for critically ill patients with ALF or ACLF who develop acute kidney injury?** | |
| **Population:** | critically ill patients with ALF or ACLF who develop acute kidney injury |
| **Intervention:** | early RRT |
| **Comparison:** | Conventional indication for RRT |
| **Main outcomes:** | Mortality; |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know | *See Appendix 1* |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know | *See Appendix 1* | From a patient safety perspective there aren’t many undesirable effects. However, from resource utilization perspective it could be different. |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Very low ○ Low ○ Moderate ○ High ○ No included studies |  | GRADE profile: very low |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability |  |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know |  |  |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies | No available studies | There is agreement that resources may be expensive and not widely available in certain resource poor regions however we acknowledge that no included studies addresses this question specifically. |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 | No available studies |  |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know |  |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know |  |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  |  |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

Appendices

Appendix 1

1. Cardoso FS, Gottfried M, Tujios S, et al. Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. Hepatology 2017.

| **Outcomes** | **With late RRT** | **With early renal replacement therapy (RRT)** | **Difference** | **Relative effect (95% CI)** |
| --- | --- | --- | --- | --- |
| Mortality | 846 per 1,000 | **630 per 1,000** (331 to 850) | **216 fewer per 1,000** (515 fewer to 4 more) | **OR 0.31** (0.09 to 1.03) |

# Appendix Table 18. EtD for vasopressors in HRS recommendation

|  |  |
| --- | --- |
| Question | |
| **Should Terlipressin vs. placebo or no intervention be used for critically ill patients with chronic liver disease who develop acute kidney injury?** | |
| **Population:** | critically ill patients with ACLF who develop acute kidney injury |
| **Intervention:** | Terlipressin |
| **Comparison:** | placebo or no intervention |
| **Main outcomes:** | Mortality; |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | *See Appendix 1* | All panelists agree 150-200 fewer/1000 would be considered large |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | *See Appendix 1* | Generally thought the undesirable effects are rare at prescribed doses.    Systematic review looked at different adverse events however not defined well. (Gluud & Israelsen cochrane reviews) |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ● Moderate ○ High ○ No included studies | *See Appendix 1* |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability |  | No important uncertainty |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know |  | It depends. For example, if patient is on the ward, then moving them to ICU to receive the medicine will increase cost. But if patient is in ICU then the additional cost is not significant. |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  | Panel members are not aware of any body of evidence. |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know |  | Unlikely that specific subgroups will be deprived from the intervention. |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | All agree |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  |  |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | **Strong recommendation for the intervention** |
| ○ | ○ | ○ | ○ | **●** |

Appendices

Appendix 1

1. Allegretti AS, Israelsen M, Krag A, et al. Terlipressin versus placebo or no intervention for people with cirrhosis and hepatorenal syndrome. Cochrane Database Syst Rev 2017;6:CD005162.

| **Outcomes** | **With placebo or no intervention** | **With Terlipressin** | **Difference** | **Relative effect (95% CI)** |
| --- | --- | --- | --- | --- |
| Mortality | 612 per 1,000 | **520 per 1,000** (447 to 600) | **92 fewer per 1,000** (165 fewer to 12 fewer) | **RR 0.85** (0.73 to 0.98) |

# Appendix Table 19. EtD for TIPS in prevention of HRS recommendation

|  |  |
| --- | --- |
| Question | |
| **Should TIPS vs. no TIPS be used for critically ill patients with chronic liver disease who develop hepatorenal syndrome?** | |
| **Population:** | critically ill patients with ACLF who develop hepatorenal syndrome |
| **Intervention:** | TIPS |
| **Comparison:** | no TIPS |
| **Main outcomes:** | Mortality; Transplant Free Survival; Severe Hepatic Encephalopathy; |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know | *See Appendix 1* | Caveat: No study had resolution of HRS as primary outcome. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know | *See Appendix 1* | Patients treated with TIPS presented a significantly higher risk of severe HE than those treated with paracentesis (39% *vs* 23%, OR = 2.18, 95%CI: 1.27-3.76, *P* = 0.005, Table [5](https://www.wjgnet.com/1007-9327/full/v20/i10/2704.htm#T5)). |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies |  | Population is refractory ascites and not critically ill patients. |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability |  |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know |  |  |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies | No available studies |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 | No available studies |  |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know |  |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | **Conditional recommendation for either the intervention or the comparison** | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○ | ○ | **●** | ○ | ○ |

Appendices

Appendix 1

1. Bai M, Qi XS, Yang ZP, et al. TIPS improves liver transplantation-free survival in cirrhotic patients with refractory ascites: an updated meta-analysis. World J Gastroenterol 2014;20(10):2704-2714.

| **Outcomes** | **With no TIPS** | **With TIPS** | **Difference** | **Relative effect (95% CI)** |
| --- | --- | --- | --- | --- |
| Mortality | 540 per 1,000 | **492 per 1,000** (378 to 632) | **49 fewer per 1,000** (162 fewer to 92 more) | **RR 0.91** (0.70 to 1.17) |
| Transplant Free Survival | 312 per 1,000 | **284 per 1,000** (234 to 343) | **28 fewer per 1,000** (78 fewer to 31 more) | **RR 0.91** (0.75 to 1.10) |
| Severe Hepatic Encephalopathy | 234 per 1,000 | **383 per 1,000** (269 to 544) | **149 more per 1,000** (35 more to 311 more) | **RR 1.64** (1.15 to 2.33) |
| Hepatorenal Syndrome | 235 per 1,000 | **90 per 1,000 (36 to 209)** | **146 fewer per 1,000 (200 fewer to 26 fewer)** | **RR 0.38 (0.16 to 0.94)** |

# Appendix Table 20. EtD for glycemic control in patients with ALF or ACLF

|  |  |
| --- | --- |
| Question | |
| **Should tight glucose control (TGC) vs. conventional glucose control (CGC) be used for patients with ALF or ACLF?** | |
| **Population:** | Patients with ALF or ACLF |
| **Intervention:** | Tight glucose control (TGC) |
| **Comparison:** | Conventional glucose control (CGC) |
| **Main outcomes:** | Mortality; Hypoglycemia; |
| **Setting:** | Intensive Care Unit (ICU) |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know | *See Appendix 1* |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know | *See Appendix 1* |  |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ● High ○ No included studies | | **Outcomes** | **Importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Mortality | CRITICAL | ⨁⨁⨁⨁ HIGHa | | Hypoglycemia | CRITICAL | ⨁⨁⨁⨁ HIGHb,c |  1. Although all RCTs were unblinded, the impact on mortality outcome is unlikely to be important, therefore, we did not lower the quality of evidence for risk of bias 2. The RR > 2, therefore, we upgraded the quality of evidence by one level 3. We lowered the quality of evidence by one level for heterogeneity, the I 2= 61%, this was not explained by subgroup analyses for risk of bias or blood glucose level target |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes |  |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ● 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 How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know |  | Insulin and medical supplies for TGC  Possible increase in LOS and neurological outcomes |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know |  |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  |  |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 |  |  | No known undesirable outcomes |
| **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 |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Strong recommendation against the intervention** | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| **●** | ○ | ○ | ○ | ○ |

Appendices

Appendix 1

1. Yamada T, Shojima N, Noma H, et al. Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. Intensive Care Med 2017;43(1):1-15.
2. Yatabe T, Inoue S, Sakaguchi M, et al. The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. Intensive Care Med 2017;43(1):16-28.

| **Outcomes** | **With Conventional glucose control (CGC)** | **With tight glucose control (TGC)** | **Difference** | **Relative effect (95% CI)** |
| --- | --- | --- | --- | --- |
| Mortality | 325 per 1,000 | **342 per 1,000** (312 to 371) | **16 more per 1,000** (13 fewer to 46 more) | **RR 1.05** (0.96 to 1.14) |
| Hypoglycemia | 150 per 1,000 | **440 per 1,000** (254 to 759) | **290 more per 1,000** (104 more to 609 more) | **RR 2.93** (1.69 to 5.06) |

# Appendix Table 21. EtD for stress dose steroids in ALF or ACLF with shock recommendation

|  |  |
| --- | --- |
| Question | |
| **Should intravenous glucocorticoids vs. no glucocorticoids be used for patents with liver failure and shock?** | |
| **Population:** | Patents with liver failure and refractory shock |
| **Intervention:** | Intravenous glucocorticoids |
| **Comparison:** | No glucocorticoids |
| **Main outcomes:** | Mortality (ICU); Mortality- indirect evidence from critically ill patients; Shock Reversal; Shock Reversal- indirect evidence; Major Adverse Events; Organ Dysfunction (SOFA score)-indirect evidence from critically ill population; |
| **Setting:** | Critical Care |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | prevalence AI in liver patients is higher than those without liver failure |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | *See Appendix 1* | Debate about whether this is a small or moderate  Panel member1 thought that shock reversal effect was large and small/trivial mortality effect, qualified as moderate effect.  Panel member2 thought overall benefit is small given small effect on mortality  Panel 3 moderate effect |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know | *See Appendix 1* |  |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies | *See Appendix 2* |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability | No research evidence to support this |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 |  | Patients V&P will likely have more weight here. consensus on Probably favours steroids |
| Resources required How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know | No cost effectiveness studies |  |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies | No cost effectiveness studies |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 | No cost effectiveness studies |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | No Evidence | Steroids are available, no strong barriers to administration.  But in Low income countries not sure, but likely feasible. |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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** |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

Appendices

Appendix 1

1. Arabi YM, Aljumah A, Dabbagh O, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. CMAJ 2010;182(18):1971-1977
2. Rochwerg B, Oczkowski SJ, Siemieniuk RAC, et al. Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis. Crit Care Med 2018;46(9):1411-1420

| **Outcomes** | **With No steroids** | **With Intravenous Steroids** | **Difference** | **Relative effect (95% CI)** |
| --- | --- | --- | --- | --- |
| Mortality (ICU) | 667 per 1,000 | **613 per 1,000** (440 to 867) | **53 fewer per 1,000** (227 fewer to 200 more) | **RR 0.92** (0.66 to 1.30) |
| Mortality- indirect evidence from critically ill patients | 286 per 1,000 | **266 per 1,000** (240 to 294) | **20 fewer per 1,000** (46 fewer to 9 more) | **RR 0.93** (0.84 to 1.03) |
| Shock Reversal | 389 per 1,000 | **614 per 1,000** (381 to 992) | **226 more per 1,000** (8 fewer to 603 more) | **RR 1.58** (0.98 to 2.55) |
| Shock Reversal- indirect evidence follow up: mean 7 days | 629 per 1,000 | **792 per 1,000** (704 to 893) | **163 more per 1,000** (75 more to 264 more) | **RR 1.26** (1.12 to 1.42) |
| Major Adverse Events | 389 per 1,000 | **642 per 1,000** (401 to 1,000) | **253 more per 1,000** (12 more to 638 more) | **RR 1.65** (1.03 to 2.64) |
| Organ Dysfunction (SOFA score)-indirect evidence from critically ill population Scale from: 0 to 24 follow up: median 7 days | The mean organ Dysfunction (SOFA score)-indirect evidence from critically ill population was **0** points | The mean organ Dysfunction (SOFA score)-indirect evidence from critically ill population in the intervention group was 1.39 points lower (1.88 lower to 0.89 lower) | MD **1.39 points lower** (1.88 lower to 0.89 lower) | - |

Appendix 2

| **Outcomes** | **Importance** | **Certainty of the evidence (GRADE)** |
| --- | --- | --- |
| Mortality (ICU) | CRITICAL | ⨁⨁◯◯ LOWa,b |
| Shock Reversal | IMPORTANT | ⨁⨁◯◯ LOWb,c |
| Major Adverse Events | CRITICAL | ⨁⨁◯◯ LOWb,d |

1. We downgraded the quality of evidence by one level for imprecision, the CI included both large harm and benefit
2. We downgraded the quality of evidence by one level for risk of bias, this trial was stopped early for futility, therefore, was judged to be at high risk of bias
3. We downgraded the quality of evidence by one level for imprecision, the CI crosses the line of unity and the number of events was small
4. We downgraded the quality of evidence by one level for imprecision, the number of events was small, therefore, the magnitude of harm could be different if we had a larger sample

# Appendix Table 22. Summary of findings table for low protein diet recommendation

Maharshi S, Sharma BC, Sachdeva S, et al. Efficacy of Nutritional Therapy for Patients With Cirrhosis and Minimal Hepatic Encephalopathy in a Randomized Trial. Clin Gastroenterol Hepatol 2016;14(3):454-460 e453; quiz e433.

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Low Protein Diet** | **Normal Protein Diet** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | very serious b | none | 5/60 (8.3%) | 9/60 (15.0%) | **RR 0.56** (0.20 to 1.56) | **66 fewer per 1,000** (from 120 fewer to 84 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Hepatic Encephalopathy** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | serious a | serious c | none | 6/38 (15.8%) | 13/35 (37.1%) | **RR 0.43** (0.18 to 1.00) | **212 fewer per 1,000** (from 305 fewer to 0 fewer) | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio

#### Explanations

a. We downgraded the quality of evidence by one level for indirectness of population and intervention, the population included non-critically ill patients with liver cirrhosis, and the intervention was administered for 6 months

b. We downgraded the quality of evidence by two levels for very serious imprecision, the CI is very wide including very large harm and very large benefit, the number of events was very small

c. We downgraded the quality of evidence by one level for serious imprecision, the CI includes both no benefit and large benefit, the number of events was small

# Appendix Table 23. EtD for EN versus PN recommendation

|  |  |
| --- | --- |
| Question | |
| **Should early enteral nutrition vs. Early PN be used for critically ill patients with acute or acute-on-chronic liver faiure?** | |
| **Population:** | critically ill patients with acute or acute-on-chronic liver failure |
| **Intervention:** | enteral nutrition |
| **Comparison:** | parenteral nutrition |
| **Main outcomes:** | Mortality; Infections; Transplant free survival; |
| **Setting:** |  |
| **Perspective:** |  |
| **Background:** |  |
| **Conflict of interest:** |  |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know | Zhang G, Zhang K, Cui W, et al. The effect of enteral versus parenteral nutrition for critically ill patients: A systematic review and meta-analysis. J Clin Anesth 2018;51:62-92     | Outcomes | **Anticipated absolute effects\* (95% CI)** | | Relative effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE) | | --- | --- | --- | --- | --- | --- | | **Risk with PN** | **Risk with EN** | | Mortality | Study population | | **OR 0.98** (0.81 to 1.18) | 6500 (23 RCTs) | ⨁⨁⨁◯ MODERATEa | | 324 per 1,000 | **320 per 1,000** (280 to 361) | | Infections | Study population | | **OR 0.59** (0.43 to 0.82) | 6075 (14 RCTs) | ⨁⨁◯◯ LOWa,b | | 79 per 1,000 | **48 per 1,000** (36 to 66) |   a.     We downgraded the quality of evidence by one level for indirectness  b.     We downgraded the quality of evidence by one level for risk of bias, most studies were unblinded and a large proportion did not properly describe randomization | Trivial effect for mortality and moderate for infections, putting them together yielding small benefit |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know | | Outcomes | **Anticipated absolute effects\* (95% CI)** | | Relative effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE) | | --- | --- | --- | --- | --- | --- | | **Risk with PN** | **Risk with EN** | | Mortality | Study population | | **OR 0.98** (0.81 to 1.18) | 6500 (23 RCTs) | ⨁⨁⨁◯ MODERATEa | | 324 per 1,000 | **320 per 1,000** (280 to 361) | | Infections | Study population | | **OR 0.59** (0.43 to 0.82) | 6075 (14 RCTs) | ⨁⨁◯◯ LOWa,b | | 79 per 1,000 | **48 per 1,000** (36 to 66) |   a.     We downgraded the quality of evidence by one level for indirectness  b.     We downgraded the quality of evidence by one level for risk of bias, most studies were unblinded and a large proportion did not properly describe randomization | Aspiration could theoretically increase but no evidence available  Hypothetical risk of inability of metabolism of macronutrients |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies | | **Outcomes** | **Importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Mortality | CRITICAL | ⨁⨁⨁◯ MODERATEa | | Infections | CRITICAL | ⨁⨁◯◯ LOWb | | Transplant free survival - not reported |  | - |  1. We downgraded the quality of evidence by one level for imprecision, the CI included both benefit and harm 2. We downgraded the quality of evidence by one level for risk of bias, unblinded trials and a subjective outcome |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability | no research evidence |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know |  | central access, TPN are more expensive  (we estimate TPN vs EN is > 200-300$/day not including CVC costs) |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies | no research evidence in this population |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ 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 | ? some available Beth will find them :) |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | No evidence | timing of intervention (early) might sometimes be less acceptable to physicians who might want to wait rather than start early |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | No evidence |  |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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** |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |