**Supplementary Table 1.** List of PICO questions

|  |  |  |  |
| --- | --- | --- | --- |
| **NEUROLOGY** | | | |
| 1. In critically ill ALF patients with high-grade encephalopathy, should we recommend using intracranial pressure monitoring? | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with acute liver failure and high-grade encephalopathy | Intracranial Pressure Monitoring | No Intracranial Pressure Monitoring | Mortality  Intracranial Hemorrhage  Infection |
| 1. In critically ill ALF patients with hyperammonenia, should we recommend using therapeutic plasma exchange | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with acute liver failure and hyperammonemia | Therapeutic plasma exchange | No therapeutic plasma exchange | Mortality  Transplant free survival  Serum ammonia levels  Organ Failure |
| 1. In critically ill ALF patients with high-grade encephalopathy, should we recommend using hypertonic saline | | | |
| Population | Intervention | Comparator | Outcomes(s) |
| Critically ill patients with acute liver failure and high-grade encephalopathy | Administration of hypertonic saline | No administration of hypertonic saline | Mortality  Intracranial hypertension  Organ Failure |
| 1. In critically ill ALF patients with high-grade encephalopathy, should we recommend using induced moderate hypothermia | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with acute liver failure and high-grade encephalopathy | Induced moderate hypothermia | Normothermia | Mortality  Intracranial hypertension  Organ Failure |
| 1. In critically ill ACLF patients with hepatic encephalopathy, should we recommend using non-absorbable disaccharides | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with acute on chronic liver failure | Non-absorbable disaccharides for hepatic encephalopathy | No intervention | Mortality  Hepatic encephalopathy  Organ Failure  Infections |
| 1. In critically ill ACLF patients with hepatic encephalopathy should we recommend using enteral polyethylene glycol (PEG) | | | |
| Population | Intervention | Comparator | Outcomes |
| Critically ill patients with ACLF | PEG for hepatic encephalopathy as an alternative to lactulose | Lactulose | Mortality  Hepatic encephalopathy  Organ Failure |
| 1. In critically ill ACLF patients with hepatic encephalopathy, should we recommend using oral rifaximin as adjunctive therapy | | | |
| Population | Intervention | Comparator | Outcomes |
| Critically ill patients with ACLF | Rifaximin as adjunctive therapy to lactulose for hepatic encephalopathy | Lactulose alone | Mortality  Hepatic encephalopathy  Organ Failure |
| 1. In critically ill ACLF patients with hepatic encephalopathy, should we recommend using L-Ornithine L- Aspartate (LOLA) | | | |
| Population | Intervention | Comparator | Outcomes |
| Critically ill patients with ACLF | L-Ornithine L- Aspartate (LOLA) for hepatic encephalopathy | No intervention | Mortality  Hepatic encephalopathy  Organ Failure |
| 1. In critically ill ACLF patients with hepatic encephalopathy should we recommend using flumazenil, zinc supplementation, glycerol phenylbutyrate, or acrabose as adjunctive therapies | | | |
| Population | Intervention | Comparator | Outcomes |
| Critically ill patients with ACLF | Flumazenil, zinc supplementation, glycerol phenylbutyrate, or acrabose as adjunctive therapies for hepatic encephalopathy | Standard therapy for hepatic encephalopathy such as lactulose | Mortality  Hepatic encephalopathy  Organ Failure |
| **INFECTIOUS DISEASES** | | | |
| 1. In critically ill ACLF patients with upper gastrointestinal bleeding should we recommend using prophylactic antibiotics | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with acute on chronic liver failure | Prophylactic antibiotics for upper gastrointestinal bleeding | No intervention | Mortality  Rebleeding  Infections |
| 1. In critically ill ACLF patients with spontaneous bacterial peritonitis, should we recommend using albumin | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with ACLF and spontaneous bacterial peritonitis | Albumin infusion | No intervention | Mortality  Organ failure |
| 1. In critically ill liver transplant recipients, should we recommend using antifungal prophylaxis | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill liver transplant recipients | Systemic antifungal prophylaxis | No systemic antifungal prophylaxis | Mortality  Fungal infections |
| 1. In critically ill ACLF patients with spontaneous bacterial peritonitis and septic shock, should we recommend starting antibiotic therapy as soon as possible after recognition. | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with ACLF, spontaneous bacterial peritonitis and septic shock | administration of antibiotic therapy as soon as possible after recognition | Delayed antibiotic therapy | Mortality  Organ Failure |
| 1. In critically ill ACLF patients with spontaneous bacterial peritonitis, should we recommend performing high volume paracentesis (LVP > 4 L) | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill ACLF and spontaneous bacterial peritonitis | Large volume paracentesis | Standard of care without large volume paracentesis | Mortality  Organ Failure |
| 1. In critically ill liver transplant recipients should we recommend using selective bowel decontamination | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill liver transplant recipients | Use of selective bowel decontamination | Not using selective bowel decontamination | Mortality  Organ Failure  Graft Dysfunction  Re-transplantation  Occurrence of resistant infections |
| 1. In critically ill ACLF patients with spontaneous bacterial peritonitis, should we recommend using broad spectrum antibiotic therapy for initial management | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with ACLF and spontaneous bacterial peritonitis | Use of broad-spectrum antibiotics as initial therapy | Narrow spectrum antibiotics as initial therapy | Mortality  Organ Failure |
| 1. In critically ill ACLF patients with spontaneous bacterial peritonitis should we recommend using Midodrine or Terlipressin | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with ACLF and spontaneous bacterial peritonitis | Use of midodrine or terlipressin | Not using midodrine or terlipressin | Mortality  Organ Failure |
| **GASTROENTEROLOGY** | | | |
| 1. In critically ill ACLF patients with portal hypertensive bleeding, should we recommend performing endoscopy within 12 hours of presentation | | | |
| Population | Intervention | Comparator | Outcomes(s) |
| Critically ill patients with ACLF and portal hypertensive gastrointestinal bleeding | Endoscopy within 12 hours of presentation | Endoscopy later than 12 hours of presentation | Mortality  Re-bleeding  Organ Failure  Infection |
| 1. In critically ill ACLF patients with portal hypertensive bleeding should we recommend using proton pump inhibitors | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with ACLF and portal hypertensive gastrointestinal bleeding | Use of proton pump inhibitors | No use of proton pump inhibitors | Mortality  Re-bleeding  Organ Failure  Infections |
| 1. In critically ill ACLF patients with portal hypertensive bleeding should we recommend using octreotide or somatostatin analogues | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with ACLF and portal hypertensive bleeding | Use of octreotide and somatostatin analogues | No use of octreotide or somatostatin analogues | Mortality  Re-bleeding  Organ Failure  Infection |
| 1. In critically ill ACLF patients with recurrent variceal bleeding, should we recommend using transjugular intrahepatic portosystemic shunt placement | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with chronic liver failure and recurrent variceal bleeding | Placement of transjugular intrahepatic portosystemic shunt (TIPS) | No placement of TIPS | Mortality  Recurrent bleeding  Encephalopathy  Organ Failure |
| 1. In critically ill ACLF patients with tense ascites should we recommend large volume paracentesis | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with ACLF and tense ascites | Large Volume Paracentesis | No large volume paracentesis | Mortality  Intra-abdominal pressure  Organ Failure |
| **PERI-OPERATIVE** | | | |
| 1. In deceased liver graft donors should we recommend using corticosteroids | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Deceased liver graft donors | administration of corticosteroids | No administration of corticosteroids | Mortality  Graft dysfunction |
| 1. In deceased liver graft donors, should we recommend using goal directed fluid management strategies | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Deceased liver graft donors | Goal directed fluid management | Standard fluid management | Mortality  Graft dysfunction |
| 1. Should we recommend using the donor risk index (DRI) to evaluate appropriateness of allograft transplantation | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Deceased liver graft donors | Use of DRI | No use of DRI | Mortality  Graft dysfunction |
| 1. In critically ill ALF or ACLF patients, should we recommend usng extracorporeal liver support | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with ALF or ACLF | Use of extracorporeal liver support | No use of extracorporeal liver support | Mortality  Transplant free survival  Organ failure |
| 1. In the liver transplant recipient, perioperatively, should we recommend using fluid restriction accompanied by vasopressor use | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Liver transplant recipients | Fluid restriction accompanied by vasopressor support | Liberal fluid administration | Mortality  Graft dysfunction  Organ failure |
| 1. In liver transplant recipients should we recommend using balanced crystalloid solutions perioperatively | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Liver transplant recipients during the perioperative period | Balanced crystalloid solution use | Use of hyperchloremic solutions | Mortality  Graft dysfunction  Organ failure |
| 1. In liver transplant recipients, should we recommend using albumin in the intraoperative period | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Liver transplant recipients | Albumin during the intraoperative period | Crystalloid in the intraoperative period | Mortality  Graft dysfunction  Organ Failure |
| 1. In the liver transplant recipient, should we recommend early extubation post-operatively | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Liver transplant recipient | Early post-operative extubation | Delayed post-operative extubation | Mortality  Graft dysfunction  Ventilator days  Organ Failure  Infections |
| 1. In the liver transplant recipient, should we recommend using invasive hemodynamic monitoring | | | |
| Population | Intervention | Comparator | Outcome(s) |
| Liver transplant recipients | Invasive hemodynamic monitoring | Non-invasive hemodynamic monitoring | Mortality  Graft dysfunction  Organ Failure |

# Neurology section

# Supplementary Table 2: In critically ill patients with ALF and high-grade encephalopathy, should we recommend intracranial pressure monitoring?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **ICP monitor** | **no Monitor** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 3 | observational studies | serious | not serious | not serious | serious a | all plausible residual confounding would suggest spurious effect, while no effect was observed | 69/178 (38.8%) | 208/525 (39.6%) | **OR 1.21** (0.84 to 1.75) | **46 more per 1,000** (from 41 fewer to 138 more) | ⨁◯◯◯ VERY LOW |  |

**CI:** Confidence interval; **OR:** Odds ratio

#### Explanations

a. We downgraded for imprecision by one point as confidence interval included both significant benefit and harm (0.84, 1.75)

## EtD: 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 |

# Supplementary Table 3a: In critically ill patients with ALF and hyperammonenia, should we recommend therapeutic plasma exchange?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interventions to Reduce ICP** | **placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality - High Volume Plasma Exchange** | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | not serious | very serious a | none | 38/92 (41.3%) | 47/90 (52.2%) | **RR 0.79** (0.58 to 1.08) | **110 fewer per 1,000** (from 219 fewer to 42 more) | ⨁⨁◯◯ LOW |  |

#### Explanations

a. We downgraded for imprecision by 2 points as confidence interval includes both significant benefit and harm and overall small sample size.

## EtD: 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 |

# Supplementary Table 3b: In critically ill patients with ALF and high-grade encephalopathy, should we recommend using hypertonic saline?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Hypertonic saline** | **control** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality of increased ICP** | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | not serious | very serious a | none | 2/15 (13.3%) | 3/15 (20.0%) | **RR 0.67** (0.13 to 3.44) | **66 fewer per 1,000** (from 174 fewer to 488 more) | ⨁⨁◯◯ LOW |  |

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

#### Explanations

a. we downgraded for imprecision by 2 points as confidence interval included both significant benefit and harm, and very small number of events and patients.

## EtD: 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 |

# Supplementary Table 3c: In critically ill patients with ALF and high-grade encephalopathy, should we recommend induced moderate hypothermia?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Interventions to Reduce ICP** | **placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality - Hypothermia Vs Normothermia - RCT** | | | | | | | | | | | | |
| 1 | randomized trials | serious a | not serious | not serious | very serious b | none | 7/17 (41.2%) | 12/26 (46.2%) | **RR 0.89** (0.44 to 1.80) | **51 fewer per 1,000** (from 258 fewer to 369 more) | ⨁◯◯◯ VERY LOW |  |
| **Mortality - Hypothermia Vs Normothermia - Observational** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | serious c | none | 37/97 (38.1%) | 456/1135 (40.2%) | **OR 0.92** (0.60 to 1.41) | **20 fewer per 1,000** (from 115 fewer to 85 more) | ⨁◯◯◯ VERY LOW |  |
| **TFS - Hypothermia - RCT** | | | | | | | | | | | | |
| 1 | randomized trials | serious a | not serious | not serious | serious c | none | 3/17 (17.6%) | 6/26 (23.1%) | **RR 1.07** (0.79 to 1.45) | **16 more per 1,000** (from 48 fewer to 104 more) | ⨁⨁◯◯ LOW |  |
| **TFS - Hypothermia - Observational** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | serious c | none | 44/97 (45.4%) | 443/1135 (39.0%) | **OR 0.77** (0.51 to 1.17) | **60 fewer per 1,000** (from 144 fewer to 38 more) | ⨁◯◯◯ VERY LOW |  |

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

#### Explanations

a. Trial stopped early for futility

b. We downgraded by two points for inconsistency as confidence interval includes both significant benefit and harm and small number of events

c. We downgraded for imprecision by one point as confidence interval includes both significant benefit and harm.

## EtD: 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 |

Supplementary Table 4: In critically ill patients with ACLF and hepatic encephalopathy, should we recommend using non-absorbable disaccharides?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Non-absorbable disaccharides** | **control** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality - All trials: prevention/acute & chronic/overt & minimal (assessed with: total number of participants who died)** | | | | | | | | | | | | |
| 24 | randomized trials | serious | not serious | serious a | not serious | none | 36/768 (4.7%) | 63/719 (8.8%) | **RR 0.59** (0.40 to 0.87) | **36 fewer per 1,000** (from 53 fewer to 11 fewer) | ⨁⨁◯◯ LOW | CRITICAL |
| **Mortality - Acute Hepatic Encephalopathy** | | | | | | | | | | | | |
| 3 | randomized trials | serious b | not serious | serious a | serious c | none | 4/54 (7.4%) | 12/48 (25.0%) | **RR 0.36** (0.14 to 0.94) | **160 fewer per 1,000** (from 215 fewer to 15 fewer) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Mortality - Overt HE Acute and Chronic** | | | | | | | | | | | | |
| 6 | randomized trials | serious b | not serious | serious a | serious d | none | 4/89 (4.5%) | 12/83 (14.5%) | **RR 0.36** (0.14 to 0.94) | **93 fewer per 1,000** (from 124 fewer to 9 fewer) | ⨁◯◯◯ VERY LOW |  |
| **Serious Adverse events - Acute HE** | | | | | | | | | | | | |
| 3 | randomized trials | serious b | not serious | serious a | serious e | none | 5/54 (9.3%) | 11/48 (22.9%) | **RR 0.40** (0.16 to 1.02) | **137 fewer per 1,000** (from 192 fewer to 5 more) | ⨁◯◯◯ VERY LOW |  |
| **Non-serious adverse events - Acute HE** | | | | | | | | | | | | |
| 1 | randomized trials | serious b | not serious | serious a | serious f | none | 1/22 (4.5%) | 3/23 (13.0%) | **RR 0.35** (0.04 to 3.10) | **85 fewer per 1,000** (from 125 fewer to 274 more) | ⨁◯◯◯ VERY LOW |  |

#### Explanations

a. Population is HE in cirrhotic patients

b. All trials were at high risk of bias for lack of blinding (1 study) and for profit funding in all 3 studies.

c. We downgraded for imprecision by 1 point as for very wide confidence interval 0.36 [ 95% CI 0.14, 0.94]

d. We downgraded for imprecision by 1 point due to small sample size, small number of events and wide confidence interval

e. We downgraded for imprecision by 2 points as confidence interval includes both significant benefit and harm 0.4 (0.16, 1.02) and very wide confidence interval.

f. We downgraded for imprecision by 2 point as confidence interval includes both significant benefit and harm 0.35 [0.04, 3.10] and very wide confidence interval.

## EtD: 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 |

# Supplementary Table 5. In critically ill patients with ACLF and hepatic encephalopathy should we recommend the use of enteral polyethylene glycol (PEG)?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Polyethylene glycol** | **Lactulose** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **HE** | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | serious a | very serious b | none | 21/23 (91.3%) | 13/25 (52.0%) | **RR 0.18** (0.05 to 0.72) | **426 fewer per 1,000** (from 494 fewer to 146 fewer) | ⨁◯◯◯ VERY LOW |  |

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

#### Explanations

a. different population: patients with cirrhosis (of 186 screened) admitted for HE.

b. we downgraded by 2 points for imprecision for very wide confidence interval and very small number of events and patients.

## 

## EtD: 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 |

# Supplementary Table 6. In critically ill patients with ACLF and hepatic encephalopathy, should we recommend the use of oral rifaximin as adjunctive therapy?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Rifaximin** | **control** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 9 | randomised trials | not serious | not serious | serious a | serious b | none | 17/305 (5.6%) | 31/277 (11.2%) | **RR 0.50** (0.31 to 0.82) | **56 fewer per 1,000** (from 77 fewer to 20 fewer) | ⨁⨁◯◯ LOW | CRITICAL |

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

#### Explanations

a. cirrhosis with minimal or overt encephalopathy

b. small number of events 48 total

## 

## EtD: 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 |

# Supplementary Table 7: In critically ill patients with ACLF and hepatic encephalopathy, should we recommend the use of L-Ornithine L- Aspartate (LOLA)?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **L-ornithine L-aspartate** | **control** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 6 | randomized trials | serious a | not serious | serious b | serious c | none | 26/303 (8.6%) | 41/294 (13.9%) | **RR 0.64** (0.40 to 1.01) | **50 fewer per 1,000** (from 84 fewer to 1 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Serious Adverse Events** | | | | | | | | | | | | |
| 6 | randomized trials | serious a | not serious | serious b | serious d | none | 29/303 (9.6%) | 45/294 (15.3%) | **RR 0.65** (0.43 to 1.00) | **54 fewer per 1,000** (from 87 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW |  |
| **Diarrhea** | | | | | | | | | | | | |
| 2 | randomized trials | serious | not serious | serious b | serious | none | 2/140 (1.4%) | 5/137 (3.6%) | **RR 0.39** (0.08 to 1.95) | **22 fewer per 1,000** (from 34 fewer to 35 more) | ⨁◯◯◯ VERY LOW |  |
| **Flatulence** | | | | | | | | | | | | |
| 1 | randomized trials | serious | not serious | serious b | serious | none | 13/98 (13.3%) | 11/95 (11.6%) | **RR 1.15** (0.54 to 2.43) | **17 more per 1,000** (from 53 fewer to 166 more) | ⨁◯◯◯ VERY LOW |  |
| **Nausea & Vomiting** | | | | | | | | | | | | |
| 3 | randomized trials | serious | not serious | serious b | serious | none | 13/183 (7.1%) | 8/175 (4.6%) | **RR 1.47** (0.66 to 3.30) | **21 more per 1,000** (from 16 fewer to 105 more) | ⨁◯◯◯ VERY LOW |  |
| **Abdominal Pain** | | | | | | | | | | | | |
| 2 | randomized trials | serious | not serious | serious b | serious | none | 3/143 (2.1%) | 5/135 (3.7%) | **RR 0.62** (0.12 to 3.10) | **14 fewer per 1,000** (from 33 fewer to 78 more) | ⨁◯◯◯ VERY LOW |  |
| **Fever** | | | | | | | | | | | | |
| 1 | randomized trials | serious | not serious | serious b | serious | none | 13/98 (13.3%) | 2/95 (2.1%) | **RR 6.30** (1.46 to 27.18) | **112 more per 1,000** (from 10 more to 551 more) | ⨁◯◯◯ VERY LOW |  |

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

#### Explanations

a. All studies are judged to be at high risk of bias mainly due to for-profit funding and unclear randomization and allocation concealment.

b. cirrhosis with encephalopathy

c. We downgraded for imprecision by 1 point as confidence interval includes both significant benefit and harm (RR 0.64, 95% CI 0.4 to 1.01)

d. We downgraded for imprecision by 1 point as confidence interval includes significant benefit and harm

## 

## EtD: 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 |

# Supplementary Table 8: In critically ill patients with ACLF and hepatic encephalopathy should we recommend using flumazenil, probiotics, zinc supplementation, glycerol phenylbutyrate, or acrabose as adjunctive therapies?

## Flumazenil: Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Flumazenial** | **control** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality (follow up: range 1 days to 2 weeks)** | | | | | | | | | | | | |
| 11 | randomized trials | serious a | not serious | serious b | serious c | none | 32/433 (7.4%) | 38/409 (9.3%) | **RR 0.75** (0.48 to 1.16) | **23 fewer per 1,000** (from 48 fewer to 15 more) | ⨁◯◯◯ VERY LOW | CRITICAL |

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

#### Explanations

a. We downgraded by 1 point for risk of bias as only 1 study was at low risk of bias.

b. cirrhosis with encephalopathy

c. We downgraded by 1 point for imprecision as confidence interval included both significant benefit and harm (RR 0.75, 95% CI 0.48 to 1.16)

## Flumazenil: EtD 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 |

## Probiotics: Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Probiotics** | **control** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality (follow up: range 2 weeks to 3 months)** | | | | | | | | | | | | |
| 7 | randomized trials | serious a | not serious | serious b | serious c | none | 6/208 (2.9%) | 10/196 (5.1%) | **RR 0.58** (0.23 to 1.44) | **21 fewer per 1,000** (from 39 fewer to 22 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Hepatic encephalopathy (assessed with: overt hepatic encephalopathy )** | | | | | | | | | | | | |
| 10 | randomized trials | serious d | not serious | not serious | serious e | none | 2/299 (0.7%) | 48/286 (16.8%) | **RR 0.29** (0.16 to 0.51) | **119 fewer per 1,000** (from 141 fewer to 82 fewer) | ⨁⨁◯◯ LOW | CRITICAL |

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

#### Explanations

a. We downgraded by 1 point for risk bias as most studies are at high risk of bias.

b. acute or chronic encephalopathy

c. We downgraded by 1 point for imprecision as confidence interval includes both significant benefit and harm RR 0.58 (0.23 to 1.44)

d. We downgraded for risk of by bias by 1 point as 6 out of 10 studies were at high risk bias and 4 were at unclear risk of bias.

e. We downgraded for imprecision by one point due to low total number of events per arm 8 and 48 in the intervention and control arms, respectively.

## Probiotics EtD: 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 |

## Zinc: Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Zinc** | **Control** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Recurrence of HE** | | | | | | | | | | | | |
| 2 | randomized trials | serious a | not serious | not serious | very serious b | none | 7/85 (8.2%) | 11/84 (13.1%) | **RR 0.64** (0.26 to 1.59) | **47 fewer per 1,000** (from 97 fewer to 77 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Serum Ammonia** | | | | | | | | | | | | |
| 2 | randomized trials | not serious | not serious | very serious c | serious d | none | 70 | 65 | - | MD **8.04 mcg/dL lower** (15.3 lower to 0.8 lower) | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Number connection test** | | | | | | | | | | | | |
| 3 | randomized trials | serious a | serious e | serious f | serious g | none | 93 | 96 | - | SMD **0.62 lower** (0.92 lower to 0.33 lower) | ⨁◯◯◯ VERY LOW | IMPORTANT |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardized mean difference

#### Explanations

a. All studies had unclear risk of bias precluding accurate evaluation.

b. We downgraded for imprecision by 2 points for overall small sample size (n=169) and events (18)

c. serum ammonia is a surrogate outcome for hepatic encephalopathy and population is different.

d. very small difference of questionable value.

e. We downgraded for imprecision by 1 point as significant heterogeneity detected (i2=60%).

f. We downgraded for indirectness by1 point as this was not the outcome of interest as well as it is not a patient-important outcome.

g. We downgraded for imprecision by 2 points for overall small sample size (n=189).

## Zinc: EtD: 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 |

## Glycerol phenylbutyrate: Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Glycerol Phenylbutyrate** | **standard medical therapy** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Number of hepatic encephalopathy events** | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | serious a | not serious | none | 35/90 (38.9%) | 57/88 (64.8%) | **RR 0.66** (0.44 to 0.81) | **220 fewer per 1,000** (from 363 fewer to 123 fewer) | ⨁⨁⨁◯ MODERATE |  |
| **Hospitalizations for HE** | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | serious a | not serious | none | 13/90 (14.4%) | 25/88 (28.4%) | **RR 0.51** (0.28 to 0.93) | **139 fewer per 1,000** (from 205 fewer to 20 fewer) | ⨁⨁⨁◯ MODERATE |  |

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

#### Explanations

a. cirrhosis with encephalopathy

## Glycerol phenylbutyrate: EtD 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** |

## Acarbose: Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Acarbose** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Serum Ammonia level** | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | very serious a | serious b | none | 55 | 52 | - | MD **22.7 mmol/L lower** (29.79 lower to 15.61 lower) | ⨁◯◯◯ VERY LOW | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. Ammonia is a surrogate outcome and very indirect to mortality outcome of interest and patient with grade 1-2 hepatic encephalopathy

b. We downgraded for imprecision by 1 point as very small sample size.

## Acarbose: EtD 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 |

# Infectious Diseases Section

# Supplementary Table 9: In critically ill patients with ACLF should and Upper Gastrointestinal Bleeding should we recommend prophylactic antibiotics?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Prophylactic Antibiotics** | **no prophylactic antibiotics** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 12 | randomized trials | not serious | not serious | not serious | serious a | none | 109/588 (18.5%) | 145/653 (22.2%) | **RR 0.79** (0.63 to 0.98) | **47 fewer per 1,000** (from 82 fewer to 4 fewer) | ⨁⨁⨁◯ MODERATE |  |
| **SBP** | | | | | | | | | | | | |
| 8 | randomized trials | not serious | not serious | not serious | serious a | none | 10/412 (2.4%) | 42/478 (8.8%) | **RR 0.29** (0.15 to 0.57) | **62 fewer per 1,000** (from 75 fewer to 38 fewer) | ⨁⨁⨁◯ MODERATE |  |
| **Bacteremia** | | | | | | | | | | | | |
| 9 | randomized trials | serious b | not serious | not serious | not serious | none | 16/459 (3.5%) | 82/528 (15.5%) | **RR 0.25** (0.15 to 0.40) | **116 fewer per 1,000** (from 132 fewer to 93 fewer) | ⨁⨁⨁◯ MODERATE |  |
| **Bacterial infection** | | | | | | | | | | | | |
| 12 | randomized trials | serious b | not serious | not serious | not serious | none | 77/588 (13.1%) | 237/653 (36.3%) | **RR 0.36** (0.27 to 0.49) | **232 fewer per 1,000** (from 265 fewer to 185 fewer) | ⨁⨁⨁◯ MODERATE |  |
| **Rebleeding** | | | | | | | | | | | | |
| 3 | randomized trials | serious b | not serious | not serious | serious a | none | 34/141 (24.1%) | 63/139 (45.3%) | **RR 0.53** (0.38 to 0.74) | **213 fewer per 1,000** (from 281 fewer to 118 fewer) | ⨁⨁◯◯ LOW |  |

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

#### Explanations

a. on trial sequential analysis (TSA), information size was not reached and the adjusted boundaries for significant was not crossed

b. most of the included studies are at high risk of bias" mainly due to blinding"

## EtD: 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 |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

# Supplementary Table 10. In critically ill patients ACLF and spontaneous bacterial peritonitis, should we recommend using albumin?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Albumin infusion** | **No albumin** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 4 | randomized trials | serious a | not serious | not serious | not serious | none | 23/144 (16.0%) | 51/144 (35.4%) | **OR 0.34** (0.19 to 0.60) | **197 fewer per 1,000** (from 260 fewer to 107 fewer) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Renal Impairment** | | | | | | | | | | | | |
| 4 | randomized trials | very serious a,b | not serious | not serious | not serious | none | 12/144 (8.3%) | 44/144 (30.6%) | **OR 0.21** (0.11 to 0.42) | **221 fewer per 1,000** (from 259 fewer to 150 fewer) | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **OR:** Odds ratio

#### Explanations

a. Based on AMSTAR 2, the review of Salerno et al 2013, had one critical weakness” Protocol was not registered before commencement of the review”)

b. Due to lack of blinding in the included trials

## EtD: 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 |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

## Supplementary Table 11: In critically ill liver transplant recipient, should we recommend antifungal prophylaxis?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Systemic Antifungal Prophylaxis** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Invasive Fungal Infection** | | | | | | | | | | | | |
| 7 | randomized trials | serious a | not serious | not serious | serious b | none | 32/395 (8.1%) | 2.0% | **OR 0.37** (0.19 to 0.72) | **13 fewer per 1,000** (from 16 fewer to 6 fewer) | ⨁⨁◯◯ LOW | CRITICAL |
| 15.0% | **89 fewer per 1,000** (from 118 fewer to 37 fewer) |
| **Mortality** | | | | | | | | | | | | |
| 7 | randomized trials | not serious | not serious | not serious | very serious c | none |  | -/0 | **OR 0.87** (0.54 to 1.39) | **1 fewer per 1,000** (from 1 fewer to 1 fewer) | ⨁⨁◯◯ LOW | CRITICAL |
| 10.0% | **12 fewer per 1,000** (from 43 fewer to 34 more) |

**CI:** Confidence interval; **OR:** Odds ratio

#### Explanations

a. Most of the included studies at high risk of bias

b. Optimal information size not met

c. Optimal information size not met, 95%CI with plausible decrease or increase in mortality outcome

## EtD: 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 |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Supplementary Table 12: In critically ill patients with ACLF with spontaneous bacterial peritonitis and septic shock, should we recommend starting antibiotic therapy as soon as possible after recognition?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Rapid antibiotics administration** | **delayed administration of an appropriate Abx** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 1 | observational studies | serious a | not serious | not serious | not serious | all plausible residual confounding would reduce the demonstrated effect |  |  | **OR 1.86** (1.10 to 3.14) | **2 fewer per 1,000** (from 3 fewer to 1 fewer) | ⨁⨁◯◯ LOW |  |

**CI:** Confidence interval; **OR:** Odds ratio

#### Explanations

a. High risk of bias on two domains included in ROBINS-I

## EtD: 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 |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

# Supplementary Table 13: In critically ill patients with ACLF and spontaneous bacterial peritonitis, should we recommend high volume paracentesis (LVP > 4 L)?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Large volume paracentesis (LVP)** | **No LVP** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 1 | randomized trials | serious a | not serious | not serious | very serious b | none | 3/21 (14.3%) | 2/19 (10.5%) | **OR 1.42** (0.21 to 9.55) | **38 more per 1,000** (from 81 fewer to 424 more) | ⨁◯◯◯ VERY LOW |  |
| **Renal impairment** | | | | | | | | | | | | |
| 1 | randomized trials | serious c | not serious | not serious | very serious b | none | 3/21 (14.3%) | 1/19 (5.3%) | **OR 3.00** (0.28 to 31.63) | **90 more per 1,000** (from 37 fewer to 585 more) | ⨁◯◯◯ VERY LOW |  |
| **Resolution of SBP** | | | | | | | | | | | | |
| 1 | randomized trials | serious c | not serious | not serious | very serious b | none | 18/21 (85.7%) | 18/19 (94.7%) | **OR 0.33** (0.03 to 3.51) | **91 fewer per 1,000** (from 597 fewer to 37 more) | ⨁◯◯◯ VERY LOW |  |

**CI:** Confidence interval; **OR:** Odds ratio

#### Explanations

a. high risk of bias in randomization and concealment

b. small sample size with wide confidence interval with plausible harm and benefit

c. high risk of bias in randomization, concealment, and blinding

## EtD: 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 |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Supplementary Table 14: In critically ill liver transplant recipients should we recommend selective bowel decontamination?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Selective bowel decontamination** | **No intervention** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 3 | randomized trials | serious a | not serious | not serious | serious b | none | 5/87 (5.7%) | 7/103 (6.8%) | **RR 0.91** (0.31 to 2.72) | **6 fewer per 1,000** (from 47 fewer to 117 more) | ⨁⨁◯◯ LOW |  |
| **Re-transplantation** | | | | | | | | | | | | |
| 2 | randomized trials | serious a | not serious | not serious | serious b | none | 4/58 (6.9%) | 6/74 (8.1%) | **RR 0.85** (0.26 to 2.85) | **12 fewer per 1,000** (from 60 fewer to 150 more) | ⨁⨁◯◯ LOW |  |
| **Graft rejection requiring medical therapy** | | | | | | | | | | | | |
| 1 | randomized trials | serious a | not serious | not serious | serious b | none | 4/32 (12.5%) | 2/31 (6.5%) | **RR 1.94** (0.38 to 9.83) | **61 more per 1,000** (from 40 fewer to 570 more) | ⨁⨁◯◯ LOW |  |
| **Graft rejection, unspecified treatment** | | | | | | | | | | | | |
| 2 | randomized trials | serious a | not serious | not serious | serious b | none | 31/47 (66.0%) | 40/64 (62.5%) | **RR 1.09** (0.85 to 1.38) | **56 more per 1,000** (from 94 fewer to 237 more) | ⨁⨁◯◯ LOW |  |
| **Infection** | | | | | | | | | | | | |
| 4 | randomized trials | serious a | not serious | not serious | serious b | none | 51/120 (42.5%) | 61/136 (44.9%) | **RR 0.94** (0.63 to 1.41) | **27 fewer per 1,000** (from 166 fewer to 184 more) | ⨁⨁◯◯ LOW |  |

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

#### Explanations

a. High quality systematic review. However, included study/trials with high risk of bias

b. 95% CI of the point estimate crossing the no effect line with plausible benefit or harm

## EtD: 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 |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Supplementary Table 15: In critically ill patients with ACLF and spontaneous bacterial peritonitis, should we recommend broad spectrum antibiotic therapy for initial management?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Quinolone** | **3rd gen. Cephalosporin** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 4 | randomized trials | serious a | not serious | not serious | serious b | none | 18/153 (11.8%) | 26/165 (15.8%) | **OR 0.74** (0.38 to 1.45) | **36 fewer per 1,000** (from 91 fewer to 56 more) | ⨁⨁◯◯ LOW |  |
| **Resolution of SBP** | | | | | | | | | | | | |
| 5 | randomized trials | serious a | not serious | not serious | serious b | none | 211/273 (77.3%) | 225/285 (78.9%) | **OR 0.90** (0.60 to 1.36) | **18 fewer per 1,000** (from 97 fewer to 47 more) | ⨁⨁◯◯ LOW |  |

**CI:** Confidence interval; **OR:** Odds ratio

#### Explanations

a. Most trials at unclear or high risk of bias (randomization, allocation concealment and blinding domains)

b. Optimal information size not met, with 95 % CI crossing no effect margin

## EtD: 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 |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

# Supplementary Table 16a: In critically ill patients with ACLF and spontaneous bacterial peritonitis should we recommend using Midodrine?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Midodrine** | **standard care (Albumin)** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality (follow up: 1 months)** | | | | | | | | | | | | |
| 1 | randomized trials | serious a | not serious | not serious | very serious b | none | 17/50 (34.0%) | 12/50 (24.0%) | **OR 1.63** (0.68 to 3.91) | **100 more per 1,000** (from 63 fewer to 313 more) | ⨁◯◯◯ VERY LOW |  |
| **Renal failure (follow up: 1 months)** | | | | | | | | | | | | |
| 1 | randomized trials | serious c | not serious | not serious | very serious b | none | 15/50 (30.0%) | 7/50 (14.0%) | **OR 2.63** (0.97 to 7.17) | **160 more per 1,000** (from 4 fewer to 399 more) | ⨁◯◯◯ VERY LOW |  |
| **Resolution of SBP** | | | | | | | | | | | | |
| 1 | randomized trials | serious c | not serious | not serious | very serious b | none | 46/50 (92.0%) | 48/50 (96.0%) | **OR 0.48** (0.08 to 2.74) | **40 fewer per 1,000** (from 302 fewer to 25 more) | ⨁◯◯◯ VERY LOW |  |

**CI:** Confidence interval; **OR:** Odds ratio

#### Explanations

a. high risk of bias (randomization not described with no concealment)

b. small sample size, wide 95% CI with plausible harm and benefit

c. high risk of bias (randomization not described with no concealment and no blinding)

## EtD: 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 |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Supplementary Table 16b: In critically ill patients with ACLF and spontaneous bacterial peritonitis should we recommend using Terlipressin?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Terlipressin** | **Standard of care** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 2 | randomized trials | serious a ,b | not serious | not serious | very serious c | none | 11/77 (14.3%) | 16/78 (20.5%) | **OR 0.66** (0.27 to 1.58) | **60 fewer per 1,000** (from 140 fewer to 85 more) | ⨁◯◯◯ VERY LOW |  |
| **Renal Failure (follow up: 1 months)** | | | | | | | | | | | | |
| 1 | randomized trials | serious a | not serious | not serious | very serious c | none | 7/50 (14.0%) | 7/50 (14.0%) | **OR 1.00** (0.32 to 3.09) | **0 fewer per 1,000** (from 90 fewer to 195 more) | ⨁◯◯◯ VERY LOW |  |
| **Resolution of SBP** | | | | | | | | | | | | |
| 2 | randomized trials | serious a ,b | not serious | not serious | very serious c | none | 70/77 (90.9%) | 66/78 (84.6%) | **OR 1.86** (0.67 to 5.15) | **65 more per 1,000** (from 60 fewer to 120 more) | ⨁◯◯◯ VERY LOW |  |

**CI:** Confidence interval; **OR:** Odds ratio

#### Explanations

a. high risk of bias (randomization not described with no concealment and no blinding)

b. high risk of bias (randomization not described with no concealment and no blinding in one trial, and second trial published as abstract with potential of outcome time reporting bias)

c. small sample size, wide 95% CI with plausible benefit and harm

## EtD: 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 |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Gastroenterology section

# Supplementary Table 17: In critically ill patients with ACLF and portal hypertensive bleeding should we recommend use of proton pump inhibitors?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **PPI** | **No PPI/Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Rebleeding** | | | | | | | | | | | | |
| 3 | randomized trials | serious | not serious | not serious | very serious | none a | 2/64 (3.1%) | 11/67 (16.4%) | **RR 0.24** (0.06 to 0.89) | **125 fewer per 1,000** (from 154 fewer to 18 fewer) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Mortality** | | | | | | | | | | | | |
| 2 | randomized trials | serious | not serious | not serious | serious | none a | 0/43 (0.0%) | 6/44 (13.6%) | **RR 0.15** (0.02 to 1.19) | **116 fewer per 1,000** (from 134 fewer to 26 more) | ⨁⨁◯◯ LOW | CRITICAL |

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

#### Explanations

a. Could not assess for publication bias due to the small number of studies identified.

## EtD: 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 |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

# Supplementary Table 18: In critically ill patients ACLF and portal hypertensive bleeding should we recommend the use of octreotide or somatostatin analogues?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Octerortide or Somatostatin Analogue (SSA)** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 23 | randomized trials | not serious | not serious | not serious | serious | none | 204/1205 (16.9%) | 244/1205 (20.2%) | **RR 0.85** (0.72 to 1.00) | **30 fewer per 1,000** (from 57 fewer to 0 fewer) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Rebleeding** | | | | | | | | | | | | |
| 6 | randomized trials | not serious | not serious | not serious | serious | none a | 60/309 (19.4%) | 72/297 (24.2%) | **RR 0.84** (0.52 to 1.37) | **39 fewer per 1,000** (from 116 fewer to 90 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Transfusions** | | | | | | | | | | | | |
| 10 | randomized trials | not serious | not serious | not serious | serious | none a | 672 | 664 | - | MD **1.01 lower** (1.3 lower to 0.73 lower) | ⨁⨁⨁◯ MODERATE | IMPORTANT |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations

a. Could not assess for publication bias due to the small number of studies identified.

## EtD: Summary of Judgements:

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

# Supplementary Table 19: In patients with chronic liver failure and recurrent variceal bleeding, should we recommend the use of transjugular intrahepatic portosystemic shunt placement?

## Evidence profile

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Early TIPS** | **Endoscopic Prophylaxis** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 11 | randomized trials | not serious | not serious a | not serious | serious | publication bias strongly suspected | 90/354 (25.4%) | 105/368 (28.5%) | **RR 0.72** (0.45 to 1.13) | **80 fewer per 1,000** (from 157 fewer to 37 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Rebleeding** | | | | | | | | | | | | |
| 11 | randomized trials | not serious | not serious | not serious | not serious | none b | 55/388 (14.2%) | 177/385 (46.0%) | **RR 0.30** (0.18 to 0.49) | **322 fewer per 1,000** (from 377 fewer to 234 fewer) | ⨁⨁⨁⨁ HIGH | CRITICAL |
| **Hepatic Encephalopathy** | | | | | | | | | | | | |
| 11 | randomized trials | not serious | not serious | not serious | serious | none b | 137/380 (36.1%) | 83/385 (21.6%) | **RR 1.67** (1.10 to 2.56) | **144 more per 1,000** (from 22 more to 336 more) | ⨁⨁⨁◯ MODERATE | IMPORTANT |

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

#### Explanations

a. I2 325 and confidence intervals not overlapping therefore not downgraded for inconsistency.

b. could not full exclude due to small number of studies

## EtD: 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 |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Peri-transplant Section

# Supplementary Table 20: In deceased liver graft donors should we recommend administration of corticosteroids?

## Evidence profile:

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Q1. Steroids** | **no Steroids** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Graft Dysfunction - Liver only** | | | | | | | | | | | | |
| 2 | randomized trials | serious | not serious | serious | serious | none | 8/91 (8.8%) | 12/92 (13.0%) | **RR 0.68** (0.30 to 1.55) | **42 fewer per 1,000** (from 91 fewer to 72 more) | ⨁◯◯◯ VERY LOW | CRITICAL |

## EtD: 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 |

# Supplementary Table 21: In deceased liver graft donors, should we recommend goal directed fluid management strategies?

## Evidence profile:

**Bibliography**: Al-Khafaji A, Elder M, Lebovitz DJ, et al. Protocolized fluid therapy in brain-dead donors: the multicenter randomized MOnIToR trial. Intensive Care Med. 2015;41(3):418-426. doi:10.1007/s00134-014-3621-0.

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Q1. Goal directed fluid management in the organ donor** | **placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality Fluid management** | | | | | | | | | | | | |
| 1 | randomized trials | serious a | not serious | serious b | serious c | none | 56/718 (7.8%) | 56/712 (7.9%) | **RR 0.99** (0.69 to 1.42) | **1 fewer per 1,000** (from 24 fewer to 33 more) | ⨁◯◯◯ VERY LOW | CRITICAL |

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

#### Explanations

a. Cannot blind LidCo but outcome assessors blind, however this could lead to more co-interventions in LiDco arm.

b. Outcome of all transplants, no data on liver only.

c. Confidence interval included significant benefit and harm.

## EtD: 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 |

# Supplementary Table 22: In critically ill patients with acute or acute on chronic liver failure, should we recommend the use of extracorporeal liver support?

## Evidence profile:

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Artifical and Bioartificial Liver Support Systems for Liver Failure** | **placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality** | | | | | | | | | | | | |
| 24 | randomized trials | not serious a | not serious | not serious | serious b | none | 337/901 (37.4%) | 403/877 (46.0%) | **RR 0.84** (0.74 to 0.96) | **74 fewer per 1,000** (from 119 fewer to 18 fewer) | ⨁⨁⨁◯ MODERATE |  |
| **Hepatic Encephalopathy** | | | | | | | | | | | | |
| 12 | randomized trials | not serious a | not serious | not serious | serious c | publication bias strongly suspected | 70/213 (32.9%) | 116/204 (56.9%) | **RR 0.71** (0.60 to 0.84) | **165 fewer per 1,000** (from 227 fewer to 91 fewer) | ⨁⨁◯◯ LOW |  |
| **Hypotension** | | | | | | | | | | | | |
| 9 | randomized trials | not serious a | not serious | serious d | serious e | none | 72/365 (19.7%) | 50/383 (13.1%) | **RR 1.46** (0.98 to 2.20) | **60 more per 1,000** (from 3 fewer to 157 more) | ⨁⨁◯◯ LOW |  |
| **Bleeding** | | | | | | | | | | | | |
| 11 | randomized trials | not serious a | not serious | not serious | serious f | none | 120/507 (23.7%) | 99/524 (18.9%) | **RR 1.21** (0.88 to 1.66) | **40 more per 1,000** (from 23 fewer to 125 more) | ⨁⨁⨁◯ MODERATE |  |
| **Thrombocytopenia** | | | | | | | | | | | | |
| 5 | randomized trials | not serious a | serious g | serious d | serious h | none | 107/284 (37.7%) | 68/280 (24.3%) | **RR 1.62** (1.00 to 2.64) | **151 more per 1,000** (from 0 fewer to 398 more) | ⨁◯◯◯ VERY LOW |  |
| **Mortality Subgroup: ALF Vs ACLF - Acute Liver Failure** | | | | | | | | | | | | |
| 12 | randomized trials | not serious a | not serious | not serious | serious i | none | 124/346 (35.8%) | 147/330 (44.5%) | **RR 0.87** (0.71 to 1.07) | **58 fewer per 1,000** (from 129 fewer to 31 more) | ⨁⨁⨁◯ MODERATE |  |
| **Mortality Subgroup: ALF Vs ACLF - Acute on Chronic Liver Failure** | | | | | | | | | | | | |
| 13 | randomized trials | not serious a | not serious | not serious | not serious | none | 194/526 (36.9%) | 236/514 (45.9%) | **RR 0.78** (0.66 to 0.93) | **101 fewer per 1,000** (from 156 fewer to 32 fewer) | ⨁⨁⨁⨁ HIGH |  |
| **Mortality Subgroup: Artificial Vs BioArtificial - Artificial** | | | | | | | | | | | | |
| 18 | randomized trials | not serious a | not serious | not serious | not serious | none | 229/630 (36.3%) | 281/616 (45.6%) | **RR 0.83** (0.71 to 0.97) | **78 fewer per 1,000** (from 132 fewer to 14 fewer) | ⨁⨁⨁⨁ HIGH |  |
| **Mortality Subgroup: Artificial Vs BioArtificial - BioArtificial** | | | | | | | | | | | | |
| 5 | randomized trials | not serious a | not serious | not serious | serious j | none | 89/242 (36.8%) | 102/228 (44.7%) | **RR 0.77** (0.54 to 1.09) | **103 fewer per 1,000** (from 206 fewer to 40 more) | ⨁⨁⨁◯ MODERATE |  |

#### Explanations

a. We did not downgrade for unblinding of intervention as it is not possible. However the outcomes are objective.

b. We downgraded for imprecision by 1 point as Trial Sequential Analysis (TSA) estimates yielded difference point estimate and a wider confidence interval; (RR .84, 95% CI .72-.97) and 95.4 %% of required information size (RIS) achieved.

c. We downgraded for imprecision by 1 point as Trial Sequential Analysis (TSA) estimates yielded difference point estimate and a wider confidence interval; 0.68 (95% CI, 0.44, 1.05) and only 35% of RIS achieved.

d. Hypotension in itself is a surrogate outcome.

e. We downgraded by 1 point for imprecision as confidence interval includes significant benefit and harm (0.98, 2.2).

f. We downgraded by 1 point for imprecision as confidence interval includes significant benefit and harm (0.88, 1.66).

g. Significant heterogeneity detected (i2 = 62%)

h. We downgraded by 1 point for imprecision as confidence interval includes significant benefit and harm (0.7, 1.09).

i. We downgraded by 1 point for imprecision as confidence interval includes significant benefit and harm (0.79, 1.10).

j. We downgraded by 1 point for imprecision as confidence interval includes significant benefit and harm (0.54, 1.09).

## EtD: 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 |

# Supplementary Table 23: In liver transplant recipients should we recommend the use of balanced crystalloid solutions perioperatively?

## Evidence profile:

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Q7. Normorchloremic** | **Hyperchloremic** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality - Cochrane Review 2017** | | | | | | | | | | | | |
| 3 | randomized trials | serious b | not serious | serious c | very serious d | none | 4/136 (2.9%) | 2/131 (1.5%) | **OR 1.85** (0.37 to 9.33) | **13 more per 1,000** (from 10 fewer to 111 more) | ⨁◯◯◯ VERY LOW |  |
| **Mortality - Rochwerg 2014 Meta-analysis** | | | | | | | | | | | | |
| 14 | randomized trials | not serious | not serious | serious e | serious f | none |  |  | **OR 0.78** (0.58 to 1.05) | **1 fewer per 1,000** (from 1 fewer to 1 fewer) | ⨁⨁◯◯ LOW |  |
| **Mortality Adjusted - Semler (NEJM) (follow up: 30 days)** | | | | | | | | | | | | |
| 1 | randomized trials | not serious | not serious | very serious a | serious g | none | 65/635 (10.2%) | 70/629 (11.1%) | **RR 0.82** (0.60 to 1.11) | **20 fewer per 1,000** (from 45 fewer to 12 more) | ⨁◯◯◯ VERY LOW |  |

#### Explanations

a. Population is general medical and surgical ICU. Also not peri-operative use or liver transplant.

b. All studies unclear risk of bias.

c. General surgical population and none included liver transplant.

d. Odds ratio included significant harm and benefit and very wide confidence interval. OR 1.85, 95% CI 0.37 to 9.33

e. Population is critically ill septic patients and not liver transplant.

f. We downgraded 1 point for imprecision as 95% confidence interval included significant benefit and harm. OR 0.78 (0.58–1.05).

g. Confidence interval includes significant benefit and harm. 0.6-1.11

## EtD: 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 |

# Supplementary Table 24: In liver transplant recipients, should we recommend the use of albumin in the intraoperative period?

## Evidence profile:

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Q8. Colloids** | **crystalloids** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Mortality - (tetrastarch, pentastarch, dextran and gelatin)** | | | | | | | | | | | | |
| 32 | randomized trials | serious a | serious b | serious c | not serious | none | 1874/8037 (23.3%) | 2070/8610 (24.0%) | **RR 0.97** (0.92 to 1.02) | **7 fewer per 1,000** (from 19 fewer to 5 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Mortality - Albumin** | | | | | | | | | | | | |
| 2 | randomized trials | not serious | not serious | serious d | serious e | none | 190/610 (31.1%) | 220/619 (35.5%) | **OR 0.81** (0.64 to 1.03) | **47 fewer per 1,000** (from 95 fewer to 7 more) | ⨁⨁◯◯ LOW |  |

#### Explanations

a. Based on GRADE recommendations, 18 studies (31 per cent) had no limitation, 16 (27 per cent) had seri- ous limitations and 25 (42 per cent) had very severe limitations.

b. Sixteen of these trials were judged as GRADE ‘limited’, based on features such as serious risk of bias, imprecision and significant heterogeneity

c. Population is critically ill, trauma and surgical patients and not specifically liver transplant patients.

d. Different patient population.

e. CI lower limit 0.64

## EtD: 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 |