eFigure 1 Editorial Desion Tree for Overviews

eFigure 2 Interventions for prevention of NEC with low certainty evidence

eFigure 3 Interventions for prevention of NEC with very low certainty evidence

eTable 1. Search Strategy

eTable 2. AMSTAR Assessments for Included Reviews

eTable 3. GRADE Assessment of Interventions for Preventing NEC (moderate certainty)

eTable 4. GRADE Assessment of Interventions for Preventing NEC (low certainty)

eTable 5. GRADE Assessment of Interventions for Preventing NEC (very low certainty)

eTable 6. GRADE Assessment of Interventions for Preventing Surgical NEC

eTable 7. GRADE Assessment of Interventions for “All-Cause Mortality” During Hospital Stay

eTable 8. GRADE Assessment of Interventions for NEC-Related Mortality

eTable 9. Summary of Findings

References to included reviews

**eFigure 1 Editorial Desion Tree for Overviews**



**eFigure 2 Interventions for prevention of NEC with low certainty evidence**

F:\umbrellar reviews\2019.3\Figures\Supplemental figures\eFigure 2 Low quality\NEC Low quality-jama pediatrics.tiff

**eFigure 3 Interventions for prevention of NEC with very low certainty evidence**F:\umbrellar reviews\2019.3\Figures\Supplemental figures\eFigure 3 very low quality\very low quality_jama pediatrics_页面_1.tiff

F:\umbrellar reviews\2019.3\Figures\Supplemental figures\eFigure 3 very low quality\very low quality_jama pediatrics_页面_2.tiff

F:\umbrellar reviews\2019.3\Figures\Supplemental figures\eFigure 3 very low quality\very low quality_jama pediatrics_页面_3.tiff

**eTable 1. Search strategy in PubMed (Modified similar strategy applied in other databases)**

|  |  |
| --- | --- |
| **#** | **Search terms** |
| 1 | "necrotising enterocolitis"[All Fields] |
| 2 | "necrotizing enterocolitis"[All Fields] |
| 3 | "necrotising"[All Fields] AND "enterocolitis"[All Fields] |
| 4 | "necrotizing"[All Fields] AND "enterocolitis"[All Fields] |
| 5 | NEC[All Fields] |
| 6 | "enterocolitis, necrotizing"[MeSH Terms] |
| 7 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 |
| 8 | "systematic review"[All Fields] |
| 9 | "systematic review"[Publication Type] |
| 10 | "systematic reviews as topic"[MeSH Terms] |
| 11 | "meta-analysis"[All Fields] |
| 12 | "meta-analysis"[Publication Type] |
| 13 | "meta-analysis as topic"[MeSH Terms] |
| 14 | #8 OR #9 OR #10 OR #11 OR #12 OR #13 |
| 15 | #7 AND #14 |

**eTable 2. AMSTAR Assessments for Included Reviews**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **REVIEW ID** | **AMSTAR CRITERIA** | | | | | | | | | | | **TOTAL**  **SCORE** | **QUALITY** |
| **“A priori”**  **design** | **Duplicate**  **selection**  **and extraction** | **Comprehensive**  **search** | **Grey literature**  **considered** | **Included**  **and excluded**  **studies**  **lists** | **Characteristics**  **of included**  **studies** | **Quality**  **assessed**  **and**  **documented** | **Quality**  **considered**  **for**  **conclusions** | **Methods**  **for**  **combining**  **studies**  **appropriate** | **Publication**  **bias**  **considered**  **or**  **assessed** | **Conflicts**  **stated** |
| Roberts 2017[1] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | 11 | Highest |
| Flenady 2014[2] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | 11 | Highest |
| Flenady 2014[3] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | 11 | Highest |
| Dodd 2013[4] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | 11 | Highest |
| Bond 2017[5] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | 11 | Highest |
| Watson 2013[6] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | 11 | Highest |
| Kenyon 2013[7] | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | **√** | 10 | High |
| Sadeghirad 2018[8] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 10 | High |
| Oddie 2017[9] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | 10 | High |
| Zhang 2014[10] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 10 | High |
| Stock 2016[11] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 10 | High |
| Saccone 2015[12] | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | **√** | 10 | High |
| Bond 2015[13] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 10 | High |
| Neilson 2014[14] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 10 | High |
| Flenady 2013[15] | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | **√** | 10 | High |
| Woudstra 2010[16] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 10 | High |
| Lemyre 2017[17] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | 10 | High |
| Hyttel-Sorensen 2017[18] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 10 | High |
| Doyle 2017[19] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | 10 | High |
| Moe-Byrne 2016[20] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | 10 | High |
| Shah 2017[21] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 10 | High |
| Oei 2017[22] |  | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | 10 | High |
| Osborn 2018[23] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | 10 | High |
| Ohlsson 2014[24] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | 10 | High |
| Doyle 2014[25] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | 10 | High |
| Aher 2014[26] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | 10 | High |
| Ohlsson 2013[27] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | 10 | High |
| Osborn 2007[28] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 10 | High |
| Ohlsson 2015[29] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | **√** | 10 | High |
| Sawh 2016[30] | **√** |  | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 9 | High |
| Shah 2017[31] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Pammi 2017[32] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Bury 2001[33] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Churchill 2002[34] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Quigley 2018[35] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Morgan 2014[36] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Morgan 2013[37] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Foster 2016[38] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Premji 2011[39] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Livingston 2015[40] |  | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 9 | High |
| Osborn 2007[41] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| van Vliet 2016[42] | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** |  | **√** | 9 | High |
| Saccone 2015[43] | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** |  | **√** | 9 | High |
| Deshmukh 2016[44] |  | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 9 | High |
| Brown 2016[45] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Kapoor 2015[46] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Foster 2015[47] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Fenton 2014[48] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Ng 2017[49] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Ng 2017[50] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Lui 2018[51] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Fogarty 2018[52] | **√** | **√** | **√** | **√** |  | **√** | **√** | **√** |  | **√** | **√** | 9 | High |
| Amissah 2018[53] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Tan-Dy 2013[54] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Malviya 2013[55] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Howlett 2012[56] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Bottino 2011[57] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Abdel-Latif 2011[58] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Soll 2010[59] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Shah 2009[60] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Ng 2008[61] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Fowlie 2010[62] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Osborn 2007[63] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Soghier 2006[64] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Simmer 2005[65] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Kabra 2005[66] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Jardine 2004[67] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Barrington 2000[68] | **√** |  | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** | 9 | High |
| Pfister 2007[69] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Osborn 2004[70] | **√** | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  | **√** | 9 | High |
| Rees 2017[71] |  | **√** | **√** |  | **√** | **√** | **√** | **√** | **√** | **√** | **√** | 9 | High |
| Miller 2018[72] | **√** | **√** | **√** |  |  | **√** | **√** | **√** | **√** |  | **√** | 8 | High |
| Mosalli 2009[73] | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** |  |  | **√** | 8 | High |
| Conde-Agudelo 2011[74] | **√** | **√** | **√** | **√** |  | **√** | **√** |  | **√** | **√** |  | 8 | High |
| Ardell 2015[75] | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  |  | **√** | 8 | High |
| Silano 2018[76] |  | **√** | **√** |  | **√** | **√** | **√** | **√** | **√** |  | **√** | 8 | High |
| Saccone 2015[77] | **√** | **√** | **√** | **√** |  | **√** | **√** |  | **√** |  | **√** | 8 | High |
| Wu 2017[78] |  | **√** | **√** |  |  | **√** | **√** | **√** | **√** | **√** | **√** | 8 | High |
| Vayalthrikkovil 2017[79] |  | **√** | **√** | **√** |  | **√** | **√** | **√** | **√** |  | **√** | 8 | High |
| Fleeman 2016[80] | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  |  | **√** | 8 | High |
| Moyses 2013[81] | **√** | **√** | **√** | **√** |  | **√** | **√** |  | **√** |  | **√** | 8 | High |
| Ibrahim 2014[82] |  | **√** | **√** | **√** | **√** | **√** | **√** |  | **√** |  | **√** | 8 | High |
| Henderson-Smart 2001[83] | **√** | **√** | **√** | **√** |  | **√** | **√** | **√** |  |  | **√** | 8 | High |
| Bell 2014[84] | **√** | **√** | **√** | **√** | **√** | **√** | **√** |  |  |  | **√** | 8 | High |
| Soll 2009[85] | **√** | **√** | **√** | **√** |  | **√** | **√** |  | **√** |  | **√** | 8 | High |
| Herrera 2007[86] | **√** | **√** | **√** | **√** |  | **√** | **√** |  |  |  | **√** | 7 | Medium |
| Bahadue 2012[87] | **√** | **√** | **√** |  | **√** | **√** | **√** |  |  |  | **√** | 7 | Medium |
| Keir 2016[88] | **√** | **√** | **√** |  |  | **√** |  | **√** | **√** |  | **√** | 7 | Medium |
| Srinivasjois 2013[89] |  | **√** | **√** | **√** |  | **√** | **√** | **√** |  |  | **√** | 7 | Medium |
| Boyd 2007[90] | **√** | **√** | **√** |  |  | **√** | **√** | **√** |  |  | **√** | 7 | Medium |
| Dempsey 2006[91] |  |  | **√** |  | **√** | **√** | **√** |  | **√** |  | **√** | 6 | Medium |
| Smithers 2008[92] |  |  | **√** |  | **√** | **√** | **√** |  | **√** |  | **√** | 6 | Medium |
| Jin 2015[93] |  | **√** |  |  | **√** | **√** | **√** |  | **√** |  | **√** | 6 | Medium |
| Huang 2018[94] |  | **√** | **√** |  |  | **√** | **√** |  | **√** |  | **√** | 6 | Medium |
| Hutzal 2008[95] |  | **√** | **√** | **√** |  | **√** |  |  | **√** | **√** |  | 6 | Medium |
| Askie 2018[96] | **√** | **√** |  |  |  | **√** | **√** |  |  |  | **√** | 5 | Medium |
| Egarter 1996[97] |  |  | **√** |  | **√** | **√** |  |  | **√** |  |  | 4 | Medium |
| Leitich 1998[98] |  |  | **√** |  | **√** | **√** | **√** |  |  |  |  | 4 | Medium |

**eTable 3. GRADE Assessment of Interventions for Preventing NEC (Moderate Certainty)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **No of Participants (studies)** Follow up | **Certainty of the evidence** (GRADE) | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
|  | |
| **Risk with Control** | **Risk difference with Intervention for preventing** (95% CI) |
| **Probiotics (A combination of species)** Sawh 2016 | 4650 (18 studies) | ⊕⊕⊕⊝ **MODERATE**1 due to risk of bias | **RR 0.41**  (0.29 to 0.56) | **58 per 1000** | **34 fewer per 1000** (from 26 fewer to 41 fewer) |
| **Antenatal corticosteroids for accelerating fetal lung maturation** Roberts 2017 | 4702 (10 studies) | ⊕⊕⊕⊝ **MODERATE**2 due to risk of bias | **RR 0.50**  (0.32 to 0.78) | **23 per 1000** | **11 fewer per 1000** (from 5 fewer to 16 fewer) |
| **Probiotics (any)** Sawh 2016 | 10520 (38 studies) | ⊕⊕⊕⊝ **MODERATE**1 due to risk of bias | **RR 0.53**  (0.42 to 0.66) | **60 per 1000** | **28 fewer per 1000** (from 20 fewer to 35 fewer) |
| **Ibuprofen for the treatment of PDA (Ibuprofen vs. indomethacin)** Ohlsson 2015 | 948 (16 studies) | ⊕⊕⊕⊝ **MODERATE**1 due to risk of bias | **RR 0.64**  (0.45 to 0.93) | **126 per 1000** | **45 fewer per 1000** (from 9 fewer to 69 fewer) |
| **Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease** Doyle 2014 | 3507 (23 studies) | ⊕⊕⊕⊝ **MODERATE**3 due to imprecision | **RR 0.87**  (0.7 to 1.08) | **92 per 1000** | **12 fewer per 1000** (from 28 fewer to 7 more) |
| **Early erythropoietin for preventing red blood cell transfusion** Ohlsson 2014 | 1347 (11 studies) | ⊕⊕⊕⊝ **MODERATE**3 due to imprecision | **RR 1.07**  (0.73 to 1.57) | **67 per 1000** | **5 more per 1000** (from 18 fewer to 38 more) |
| **Prophylactic intravenous indomethacin (Prophylactic indomethacin vs. control)** Fowlie Peter 2010 | 2401 (12 studies) | ⊕⊕⊕⊝ **MODERATE**3 due to imprecision | **RR 1.09**  (0.82 to 1.46) | **63 per 1000** | **6 more per 1000** (from 11 fewer to 29 more) |
| \*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  **CI:** Confidence interval; **RR:** Risk ratio; | | | | | |
| GRADE Working Group grades of evidence **High certainty:** Further research is very unlikely to change our confidence in the estimate of effect.  **Moderate certainty:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low certainty:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low certainty:** We are very uncertain about the estimate. | | | | | |
| 1 Blinding of the healthcare provider and blinding of outcome assessment unclear 2 Allocation concealment is a problem 3 Wide confidence interval | | | | | |

**eTable 4. GRADE Assessment of Interventions for Preventing NEC (Low Certainty)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **No of Participants (studies)** Follow up | **Certainty of the evidence** (GRADE) | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
|  | |
| **Risk with Control** | **Risk difference with Intervention for preventing** (95% CI) |
| **Multiple vs single dose surfactant** Soll 2009 | 1169 (2 studies) | ⊕⊕⊝⊝ **LOW**1,2 due to risk of bias, publication bias | **RR 0.18**  (0.07 to 0.44) | **51 per 1000** | **42 fewer per 1000** (from 29 fewer to 48 fewer) |
| **Calcium channel blockers for inhibiting preterm labour and birth (Calcium channel blockers vs. betamimetics)** Flenady 2014 | 490 (5 studies) | ⊕⊕⊝⊝ **LOW**2,3 due to risk of bias, publication bias | **RR 0.21**  (0.05 to 0.96) | **33 per 1000** | **26 fewer per 1000** (from 1 fewer to 32 fewer) |
| **Nifedipine for preterm labor (Nifedipine vs. β2-adrenergic-receptor agonists)** Conde-Agudelo 2011 | 485 (5 studies) | ⊕⊕⊝⊝ **LOW**2,3 due to risk of bias, publication bias | **RR 0.21**  (0.05 to 0.94) | **34 per 1000** | **27 fewer per 1000** (from 2 fewer to 32 fewer) |
| **Early volume expansions (Fresh frozen plasma vs. no treatment)** Osborn 2004 | 515 (1 study) | ⊕⊕⊝⊝ **LOW**2,4 due to risk of bias, publication bias | **RR 0.22**  (0.06 to 0.74) | **54 per 1000** | **42 fewer per 1000** (from 14 fewer to 51 fewer) |
| **Prenatal progesterone for preventing preterm birth [progesterone vs placebo: previous history spontaneous preterm birth (singletons)]** Dodd 2013 | 1170 (3 studies) | ⊕⊕⊝⊝ **LOW**2,3 due to risk of bias, publication bias | **RR 0.30**  (0.1 to 0.89) | **20 per 1000** | **14 fewer per 1000** (from 2 fewer to 18 fewer) |
| **Albumin infusion** Jardine 2004 | 24 (1 study) | ⊕⊕⊝⊝ **LOW**2,5 due to imprecision, publication bias | **RR 0.33**  (0.01 to 7.45) | **83 per 1000** | **56 fewer per 1000** (from 82 fewer to 537 more) |
| **Postnatal thyroid hormones for transient hypothyroxinaemia** Osborn 2007 | 23 (1 study) | ⊕⊕⊝⊝ **LOW**2,5 due to imprecision, publication bias | **RR 0.36**  (0.02 to 8.04) | **83 per 1000** | **53 fewer per 1000** (from 82 fewer to 587 more) |
| **Arginine supplementation**  Shah 2017 | 285 (3 studies) | ⊕⊕⊝⊝ **LOW**2,6 due to imprecision, publication bias | **RR 0.38**  (0.23 to 0.64) | **303 per 1000** | **188 fewer per 1000** (from 109 fewer to 234 fewer) |
| **Enteral antibiotics** Bury 2001 | 456 (5 studies) | ⊕⊕⊝⊝ **LOW**2,3,7 due to risk of bias, publication bias | **RR 0.47**  (0.28 to 0.78) | **173 per 1000** | **92 fewer per 1000** (from 38 fewer to 125 fewer) |
| **Human milk feeding (Higher vs. lower dose human milk intake)** Miller 2018 | 1116 (4 studies) | ⊕⊕⊝⊝ **LOW**2,9 due to inconsistency, publication bias | **RR 0.54**  (0.28 to 1.02) | **94 per 1000** | **43 fewer per 1000** (from 68 fewer to 2 more) |
| **Protein containing synthetic surfactant vs. animal derived surfactant** Pfister 2007 | 1030 (2 studies) | ⊕⊕⊝⊝ **LOW**2,8 due to inconsistency, publication bias | **RR 0.60**  (0.42 to 0.86) | **139 per 1000** | **55 fewer per 1000** (from 19 fewer to 80 fewer) |
| **Probiotics (Lactobacillus)** Sawh 2016 | 2596 (8 studies) | ⊕⊕⊝⊝ **LOW**2,4 due to risk of bias, publication bias | **RR 0.61**  (0.4 to 0.95) | **41 per 1000** | **16 fewer per 1000** (from 2 fewer to 25 fewer) |
| **Omega-3 in reducing the incidence of recurrent preterm birth** Saccone 2015 | 837 (1 study) | ⊕⊕⊝⊝ **LOW**2,3,5 due to imprecision, publication bias | **RR 0.72**  (0.16 to 3.2) | **10 per 1000** | **3 fewer per 1000** (from 8 fewer to 21 more) |
| **Glutamine supplementation**  Moe-Byrne 2016 | 2849 (11 studies) | ⊕⊕⊝⊝ **LOW**5,13 due to imprecision, publication bias | **RR 0.83**  (0.66 to 1.06) | **95 per 1000** | **16 fewer per 1000** (from 32 fewer to 6 more) |
| **Delayed (≥ 30 seconds) vs. early (<30 seconds) clamping**  Fogarty 2018 | 2397 (12 studies) | ⊕⊕⊝⊝ **LOW**3,5,11 due to risk of bias, imprecision | **RR 0.88**  (0.65 to 1.18) | **-** | **-** |
| **Higher vs. lower amino acid intake** Osborn 2018 | 1301 (14 studies) | ⊕⊕⊝⊝ **LOW**3,5,10 due to risk of bias, imprecision | **RR 1**  (0.68 to 1.47) | **73 per 1000** | **0 fewer per 1000** (from 23 fewer to 34 more) |
| **Late (> 7 days) systemic postnatal corticosteroids**  Doyle 2017 | 1016 (9 studies) | ⊕⊕⊝⊝ **LOW**2,5 due to imprecision, publication bias | **RR 1.03**  (0.61 to 1.74) | **47 per 1000** | **1 more per 1000** (from 18 fewer to 35 more) |
| **Slow (up to 24 mL/kg/d) vs. faster rates of advancement of enteral feed volumes** Oddie 2017 | 3742 (10 studies) | ⊕⊕⊝⊝ **LOW**3,5 due to risk of bias, imprecision | **RR 1.07**  (0.83 to 1.39) | **55 per 1000** | **4 more per 1000** (from 9 fewer to 21 more) |
| **Prophylactic protein free synthetic surfactant** Soll 2010 | 1543 (7 studies) | ⊕⊕⊝⊝ **LOW**2,5 due to imprecision, publication bias | **RR 1.11**  (0.78 to 1.59) | **68 per 1000** | **7 more per 1000** (from 15 fewer to 40 more) |
| **Omega-3 long-chain polyunsaturated fatty acids for extremely preterm infants** Zhang 2014 | 3343 (10 studies) | ⊕⊕⊝⊝ **LOW**4,5 due to risk of bias, imprecision | **RR 1.17**  (0.77 to 1.79) | **28 per 1000** | **5 more per 1000** (from 7 fewer to 22 more) |
| **Prebiotic supplementation** Srinivasjois 2013 | 335 (5 studies) | ⊕⊕⊝⊝ **LOW**2,5 due to imprecision, publication bias | **RR 1.24**  (0.56 to 2.72) | **58 per 1000** | **14 more per 1000** (from 26 fewer to 100 more) |
| **Animal derived surfactant vs. protein free synthetic surfactant** Ardell 2015 | 3462 (8 studies) | ⊕⊕⊝⊝ **LOW**2,3 due to risk of bias, publication bias | **RR 1.38**  (1.08 to 1.76) | **59 per 1000** | **22 more per 1000** (from 5 more to 45 more) |
| **Multi-nutrient fortification of human milk for preterm infants (Fortified breast milk vs. unfortified breast milk)** Brown 2016 | 882 (11 studies) | ⊕⊕⊝⊝ **LOW**5,12 due to risk of bias, imprecision | **RR 1.57**  (0.76 to 3.23) | **25 per 1000** | **14 more per 1000** (from 6 fewer to 57 more) |
| **Formula milk vs. donor breast milk** Quigley 2018 | 1605 (8 studies) | ⊕⊕⊝⊝ **LOW**2,4 due to risk of bias, publication bias | **RR 1.87**  (1.23 to 2.85) | **37 per 1000** | **33 more per 1000** (from 9 more to 69 more) |
| **Prolonged vs. short course of indomethacin** Herrera 2007 | 310 (4 studies) | ⊕⊕⊝⊝ **LOW**2,3 due to risk of bias, publication bias | **RR 1.87**  (1.07 to 3.27) | **90 per 1000** | **79 more per 1000** (from 6 more to 205 more) |
| **Antibiotics for preterm rupture of membranes (Co-amoxiclav)** Kenyon 2013 | 1880 (2 studies) | ⊕⊕⊝⊝ **LOW**4,14,15 due to risk of bias, publication bias | **RR 4.72**  (1.57 to 14.23) | **5 per 1000** | **17 more per 1000** (from 3 more to 62 more) |
| \*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  **CI:** Confidence interval; **RR:** Risk ratio; | | | | | |
| GRADE Working Group grades of evidence **High certainty:** Further research is very unlikely to change our confidence in the estimate of effect.  **Moderate certainty:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low certainty:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low certainty:** We are very uncertain about the estimate. | | | | | |
| 1 Allocation concealment is a problem 2 Less than 10 trials 3 Blinding is a problem 4 Blinding of the healthcare provider and blinding of outcome assessment unclear 5 Wide confidence interval 6 Sample size is very small 7 Method of randomization is not clear 8 I2 is more than 50% 9 Moderate heterogeneity  10 Incomplete outcome data 11 Lack of precision and the potential for new studies to change the estimate of effect 12 Uncertainty about methods used to generate random sequence, conceal allocation and blind assessments in most trials 13 Unexplained heterogeneity and funnel plot asymmetry 14 Total number is more than 300, and with significant effect 15 Only two studies for this outcome | | | | | |

**eTable 5. GRADE Assessment of Interventions for Preventing NEC (Very Low Certainty)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **No of Participants (studies)** Follow up | **Certainty of the evidence** (GRADE) | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
|  | |
| **Risk with Control** | **Risk difference with Intervention for preventing** (95% CI) |
| **Lactoferrin plus probiotics vs. placebo** Pammi 2017 | 496 (1 study) | ⊕⊝⊝⊝ **VERY LOW**1,3,23 due to risk of bias, imprecision, publication bias | **RR 0.04**  (0 to 0.62) | **54 per 1000** | **52 fewer per 1000** (from 21 fewer to 54 fewer) |
| **Calcium channel blockers for inhibiting preterm labour and birth (Calcium channel blockers vs. oxytocin receptor antagonists)** Flenady 2014 | 179 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.1**  (0.01 to 1.88) | **47 per 1000** | **42 fewer per 1000** (from 46 fewer to 41 more) |
| **Human milk feeding (Exclusive human milk vs. exclusive preterm formula)**  Miller 2018 | 53 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,7 due to imprecision, publication bias | **RR 0.17**  (0.02 to 1.32) | **208 per 1000** | **173 fewer per 1000** (from 204 fewer to 67 more) |
| **Intravenous in-line filter vs. no filter** Foster 2015 | 88 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,7,24 due to risk of bias, imprecision, publication bias | **RR 0.2**  (0.01 to 4.05) | **45 per 1000** | **36 fewer per 1000** (from 45 fewer to 139 more) |
| **Donor breast milk vs. infant formula** Boyd 2007 | 268 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**1,3,4,6 due to risk of bias, imprecision, publication bias | **RR 0.21**  (0.06 to 0.76) | **85 per 1000** | **68 fewer per 1000** (from 21 fewer to 80 fewer) |
| **Oxytocin receptor antagonists vs. placebo for inhibiting preterm labour** Flenady 2014 | 559 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.21**  (0.02 to 1.76) | **18 per 1000** | **14 fewer per 1000** (from 17 fewer to 13 more) |
| **Corticosteroids for HELLP (Any corticosteroid vs. placebo or control)** Woudstra 2010 | 33 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.21**  (0.01 to 4.1) | **118 per 1000** | **93 fewer per 1000** (from 116 fewer to 365 more) |
| **Calcium channel blockers for inhibiting preterm labour and birth (Higher vs. lower dose calcium channel blockers)** Flenady 2014 | 100 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.22**  (0.01 to 4.39) | **38 per 1000** | **30 fewer per 1000** (from 38 fewer to 130 more) |
| **Multiple vs. single lumen umbilical venous catheters** Kabra 2005 | 36 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.24**  (0.01 to 5.57) | **67 per 1000** | **51 fewer per 1000** (from 66 fewer to 305 more) |
| **Prophylactic surgical ligation of PDA** Mosalli 2009 | 84 (1 study) | ⊕⊝⊝⊝ **VERY LOW**1,3,4,5 due to risk of bias, imprecision, publication bias | **RR 0.25**  (0.08 to 0.83) | **295 per 1000** | **222 fewer per 1000** (from 50 fewer to 272 fewer) |
| **Insulin infusion for treatment of neonatal hyperglycemia** Bottino 2011 | 23 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,9,10 due to risk of bias, imprecision, publication bias | **RR 0.31**  (0.01 to 6.85) | **91 per 1000** | **63 fewer per 1000** (from 90 fewer to 532 more) |
| **Lactase**  Tan-Dy 2013 | 130 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,11 due to risk of bias, imprecision, publication bias | **RR 0.32**  (0.01 to 7.79) | **16 per 1000** | **11 fewer per 1000** (from 15 fewer to 106 more) |
| **Postnatal thyroid hormones for infants < 37 w in the early neonatal period (< 48 hours) with suspected RDS** Osborn 2007 | 44 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,12,13 due to risk of bias, imprecision, publication bias | **RR 0.33**  (0.01 to 7.76) | **45 per 1000** | **30 fewer per 1000** (from 45 fewer to 307 more) |
| **17-alpha-hydroxyprogesterone caproate for maintenance tocolysis** Saccone 2015 | 233 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.34**  (0.05 to 2.13) | **34 per 1000** | **23 fewer per 1000** (from 32 fewer to 39 more) |
| **Probiotics (Bifidobacterium)** Sawh 2016 | 2056 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**1,2,3 due to risk of bias, inconsistency, publication bias | **RR 0.37**  (0.14 to 0.97) | **100 per 1000** | **63 fewer per 1000** (from 3 fewer to 86 fewer) |
| **Adjunctive antibiotic treatment in preterm labor** Egarter 1996 | 446 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9,10 due to risk of bias, imprecision, publication bias | **RR 0.38**  (0.14 to 1.08) | **48 per 1000** | **30 fewer per 1000** (from 42 fewer to 4 more) |
| **Heated humidified high-flow nasal cannula vs. nasal continuous positive airway pressure**  Fleeman 2016 | 435 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.41**  (0.15 to 1.14) | **56 per 1000** | **33 fewer per 1000** (from 47 fewer to 8 more) |
| **Betamimetics vs. placebo for inhibiting preterm labor** Neilson 2014 | 149 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.42**  (0.06 to 2.78) | **41 per 1000** | **24 fewer per 1000** (from 38 fewer to 72 more) |
| **Restricted vs. liberal water intakes** Bell 2014 | 526 (4 studies) | ⊕⊝⊝⊝ **VERY LOW**1,2,3 due to risk of bias, inconsistency, publication bias | **RR 0.43**  (0.21 to 0.87) | **91 per 1000** | **52 fewer per 1000** (from 12 fewer to 72 fewer) |
| **Early vs. late parenteral nutrition** Moyses 2013 | 2 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,14 due to risk of bias, imprecision, publication bias | **OR 0.52**  (0.12 to 2.16) | **1000 per 1000** | **-** |
| **Erythromycin for the prevention feeding intolerance** Ng 2008 | 149 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.59**  (0.11 to 3.01) | **51 per 1000** | **21 fewer per 1000** (from 46 fewer to 103 more) |
| **Transpyloric vs. gastric tube feeding** Watson 2013 | 298 (7 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9,10 due to risk of bias, imprecision, publication bias | **RR 0.63**  (0.26 to 1.53) | **76 per 1000** | **28 fewer per 1000** (from 56 fewer to 40 more) |
| **Calcium channel blockers vs. magnesium sulphate** Flenady 2014 | 360 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.64**  (0.13 to 3.2) | **26 per 1000** | **9 fewer per 1000** (from 22 fewer to 56 more) |
| **Early volume expansion (Volume vs. no treatment)** Osborn 2004 | 776 (1 study) | ⊕⊝⊝⊝ **VERY LOW**1,3,5 due to risk of bias, imprecision, publication bias | **RR 0.64**  (0.32 to 1.27) | **54 per 1000** | **20 fewer per 1000** (from 37 fewer to 15 more) |
| **Continuous positive airway pressure vs. theophylline**  Henderson-Smart 2001 | 32 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.64**  (0.06 to 6.39) | **111 per 1000** | **40 fewer per 1000** (from 104 fewer to 599 more) |
| **Calcium channel blockers for inhibiting preterm labour and birth (Calcium channel blockers vs. non-steroidal anti-inflammatory drugs)** Flenady 2014 | 160 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.68**  (0.14 to 3.42) | **50 per 1000** | **16 fewer per 1000** (from 43 fewer to 120 more) |
| **Protiotics (Saccharomyces boulardii)** Sawh 2016 | 357 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**1,3,5 due to risk of bias, imprecision, publication bias | **RR 0.72**  (0.33 to 1.54) | **76 per 1000** | **21 fewer per 1000** (from 51 fewer to 41 more) |
| **Early vs. late iron supplementation**  Jin 2015 | 205 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9,10 due to risk of bias, imprecision, publication bias | **OR 0.755**  (0.227 to 2.506) | **66 per 1000** | **15 fewer per 1000** (from 50 fewer to 84 more) |
| **Planned early birth vs. expectant management** Bond 2017 | 2842 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9,10 due to risk of bias, imprecision, publication bias | **RR 0.81**  (0.25 to 2.62) | **4 per 1000** | **1 fewer per 1000** (from 3 fewer to 6 more) |
| **Early introduction of lipids to parenterally-fed preterm infants** Simmer 2005 | 204 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9,10 due to risk of bias, imprecision, publication bias | **RR 0.82**  (0.34 to 1.98) | **92 per 1000** | **17 fewer per 1000** (from 61 fewer to 90 more) |
| **Cerebral near-infrared spectroscopy monitoring for prevention of brain injury** Hyttel-Sorensen 2017 | 2 (1 study) | ⊕⊝⊝⊝ **VERY LOW**7,15,16 due to risk of bias, inconsistency, indirectness, imprecision | **RR 0.83**  (0.33 to 1.94) | **1000 per 1000** | **170 fewer per 1000** (from 670 fewer to 940 more) |
| **Oral immunoglobulin** Foster 2016 | 1840 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**2,3,5,25 due to risk of bias, inconsistency, imprecision, publication bias | **RR 0.84**  (0.57 to 1.25) | **55 per 1000** | **9 fewer per 1000** (from 24 fewer to 14 more) |
| **Paracetamol vs. ibuprofen**  Huang 2018 | 527 (4 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.86**  (0.41 to 1.81) | **57 per 1000** | **8 fewer per 1000** (from 34 fewer to 46 more) |
| **Nasal intermittent positive pressure ventilation vs. nasal continuous positive airway pressure** Lemyre 2017 | 1214 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,21 due to risk of bias, imprecision, publication bias | **RR 0.87**  (0.64 to 1.19) | **127 per 1000** | **16 fewer per 1000** (from 46 fewer to 24 more) |
| **Late erythropoietin for preventing red blood cell transfusion** Aher 2014 | 646 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.88**  (0.46 to 1.69) | **52 per 1000** | **6 fewer per 1000** (from 28 fewer to 36 more) |
| **Delayed (≥4d) vs. early introduction of progressive enteral feeding (24 mL/kg/d)**  Morgan 2014 | 1092 (8 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.93**  (0.64 to 1.34) | **96 per 1000** | **7 fewer per 1000** (from 34 fewer to 32 more) |
| **Antibiotics (women between 22 and 34 w for preterm premature rupture of membranes** Hutzal 2008 | 5193 (8 studies) | ⊕⊝⊝⊝ **VERY LOW**5,9 due to risk of bias, inconsistency, imprecision | **OR 0.93**  (0.66 to 1.3) | **39 per 1000** | **3 fewer per 1000** (from 13 fewer to 11 more) |
| **Prenatal administration of progesterone for preventing preterm birth (Progesterone vs. placebo in multiple pregnancy)** Dodd 2013 | 5059 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.94**  (0.5 to 1.75) | **8 per 1000** | **0 fewer per 1000** (from 4 fewer to 6 more) |
| **Antibiotic treatment plus glucocorticoids vs only antibiotic treatment** Leitich 1998 | 998 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.94**  (0.47 to 1.9) | **70 per 1000** | **4 fewer per 1000** (from 37 fewer to 63 more) |
| **Surgical vs. medical treatment with cyclooxygenase inhibitors for symptomatic PDA** Malviya 2013 | 154 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.95**  (0.29 to 3.15) | **67 per 1000** | **3 fewer per 1000** (from 47 fewer to 143 more) |
| **Lactoferrin vs. placebo**  Pammi 2017 | 4460 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,10 due to risk of bias, imprecision, publication bias | **RR 0.95**  (0.72 to 1.24) | **46 per 1000** | **2 fewer per 1000** (from 13 fewer to 11 more) |
| **Inhaled vs. systemic corticosteroids** Shah 2017 | 368 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.96**  (0.5 to 1.85) | **96 per 1000** | **4 fewer per 1000** (from 48 fewer to 82 more) |
| **Lower (FiO2 < 0.4) vs. higher (FiO2 ≥ 0.4) oxygen concentration for preterm infants required resuscitation at birth** Lui 2018 | 807 (8 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,26 due to risk of bias, imprecision, publication bias | **RR 0.98**  (0.51 to 1.87) | **47 per 1000** | **1 fewer per 1000** (from 23 fewer to 41 more) |
| **Human and bovine colostrum** Sadeghirad 2018 | 345 (7 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,22 due to risk of bias, imprecision, publication bias | **RR 0.99**  (0.48 to 2.02) | **94 per 1000** | **1 fewer per 1000** (from 49 fewer to 95 more) |
| **Surfactant administration via a thin endotracheal catheter vs. traditional administration** Wu 2017 | 631 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 0.99**  (0.6 to 1.62) | **85 per 1000** | **1 fewer per 1000** (from 34 fewer to 53 more) |
| **Antistaphylococcal immunoglobulins to prevent staphylococcal infection （NEC Stage 2）** Shah 2009 | 2488 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**2,3,5 due to inconsistency, imprecision, publication bias | **RR 1.0**  (0.73 to 1.38) | **61 per 1000** | **0 fewer per 1000** (from 16 fewer to 23 more) |
| **Early vs. delayed selective surfactant treatment** Bahadue Felicia 2012 | 3545 (5 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 1.01**  (0.73 to 1.38) | **40 per 1000** | **0 more per 1000** (from 11 fewer to 15 more) |
| **Prophylactic antibiotics for inhibiting preterm labour with intact membrane (Any antibiotics vs. no antibiotics)** Flenady 2013 | 6880 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9,17 due to risk of bias, imprecision, publication bias | **RR 1.06**  (0.64 to 1.73) | **13 per 1000** | **1 more per 1000** (from 5 fewer to 10 more) |
| **Early volume expansion (Gelatin vs. no treatment)** Osborn 2004 | 519 (1 study) | ⊕⊝⊝⊝ **VERY LOW**1,3,5 due to risk of bias, imprecision, publication bias | **RR 1.06**  (0.52 to 2.15) | **54 per 1000** | **3 more per 1000** (from 26 fewer to 62 more) |
| **Early trophic feeding vs. enteral fasting**  Morgan 2013 | 748 (9 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,6,9 due to risk of bias, imprecision, publication bias | **RR 1.07**  (0.67 to 1.7) | **80 per 1000** | **6 more per 1000** (from 26 fewer to 56 more) |
| **Intravenous immunoglobulin for preventing infection** Ohlsson 2013 | 4081 (7 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 1.08**  (0.89 to 1.32) | **85 per 1000** | **7 more per 1000** (from 9 fewer to 27 more) |
| **Continuous nasogastric milk feeding vs. intermittent bolus milk feeding** Premji 2011 | 465 (5 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 1.09**  (0.58 to 2.07) | **65 per 1000** | **6 more per 1000** (from 27 fewer to 70 more) |
| **Hydrolysed vs. non-hydrolysed formula** Ng 2017 | 385 (5 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,27 due to risk of bias, imprecision, publication bias | **RR 1.10**  (0.36 to 3.34) | **27 per 1000** | **3 more per 1000** (from 17 fewer to 63 more) |
| **Protein supplementation of human milk**  Amissah 2018 | 76 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,18,19 due to risk of bias, imprecision, publication bias | **RR 1.11**  (0.07 to 18.49) | **25 per 1000** | **3 more per 1000** (from 23 fewer to 437 more) |
| **Parenteral fish oil lipid emulsions vs. soybean-based lipid emulsions** Vayalthrikkovil 2017 | 386 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 1.13**  (0.6 to 2.12) | **85 per 1000** | **11 more per 1000** (from 34 fewer to 96 more) |
| **Long-chain polyunsaturated fatty acid supplementation of preterm infants on disease risk and neurodevelopment** Smithers 2008 | 1333 (5 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9,10 due to risk of bias, imprecision, publication bias | **RR 1.13**  (0.62 to 2.04) | **46 per 1000** | **6 more per 1000** (from 18 fewer to 48 more) |
| **Nifedipine maintenance tocolysis** van Vliet 2016 | 895 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9,10 due to risk of bias, imprecision, publication bias | **RR 1.15**  (0.5 to 2.65) | **16 per 1000** | **2 more per 1000** (from 8 fewer to 26 more) |
| **Inositol for respiratory distress syndrome** Howlett 2012 | 355 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,8 due to risk of bias, imprecision, publication bias | **RR 1.17**  (0.51 to 2.7) | **51 per 1000** | **9 more per 1000** (from 25 fewer to 87 more) |
| **Cromolyn sodium for the prevention of chronic lung disease in preterm infants** Ng 2017 | 64 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,8,9 due to risk of bias, imprecision, publication bias | **RR 1.25**  (0.37 to 4.24) | **125 per 1000** | **31 more per 1000** (from 79 fewer to 405 more) |
| **High catheter position vs. low position** Barrington 2000 | 1569 (5 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 1.34**  (0.79 to 2.25) | **29 per 1000** | **10 more per 1000** (from 6 fewer to 36 more) |
| **Alternative lipid emulsions vs. pure soy oil based lipid emulsions for parenterally fed preterm infants** Kapoor 2015 | 314 (4 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 1.35**  (0.68 to 2.67) | **69 per 1000** | **24 more per 1000** (from 22 fewer to 116 more) |
| **Immediate vs. deferred delivery of the preterm baby with suspected fetal compromise** Stock 2016 | 576 (1 study) | ⊕⊝⊝⊝ **VERY LOW**5,9,20 due to risk of bias, imprecision, publication bias | **RR 1.44**  (0.71 to 2.93) | **43 per 1000** | **19 more per 1000** (from 12 fewer to 82 more) |
| **Red blood cell transfusions [Liberal (greater volume and/or number of RBC transfusions) vs. restrictive transfusion]** Keir 2016 | 887 (5 studies) | ⊕⊝⊝⊝ **VERY LOW**1,3,5 due to risk of bias, imprecision, publication bias | **RR 1.45**  (0.91 to 2.33) | **6 per 100** | **3 more per 100** (from 1 fewer to 8 more) |
| **Human milk feeding (Unpasteurized vs pasteurized human milk)**  Miller 2018 | 303 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,7 due to imprecision, publication bias | **RR 1.45**  (0.64 to 3.3) | **59 per 1000** | **27 more per 1000** (from 21 fewer to 136 more) |
| **Low (≤0.3) vs. high (≥0.6) FiO2 resuscitation** Oei 2017 | 483 (7 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 1.61**  (0.77 to 3.36) | **29 per 1000** | **18 more per 1000** (from 7 fewer to 68 more) |
| **Restrictive vs. liberal red blood cell transfusion thresholds** Ibrahim 2014 | 590 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 1.62**  (0.83 to 3.13) | **44 per 1000** | **27 more per 1000** (from 7 fewer to 93 more) |
| **Meconium evacuation for facilitating feed tolerance** Deshmukh 2016 | 442 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 1.71**  (0.63 to 4.65) | **73 per 1000** | **52 more per 1000** (from 27 fewer to 267 more) |
| **Early volume expansion [Colloid (albumin) vs. crystalloid (saline) in hypotensive infants]** Osborn 2004 | 63 (1 study) | ⊕⊝⊝⊝ **VERY LOW**1,3,5,7 due to risk of bias, imprecision, publication bias | **RR 1.94**  (0.38 to 9.83) | **65 per 1000** | **61 more per 1000** (from 40 fewer to 570 more) |
| **Glycerin enemas and suppositories (NEC ≥ Bell Stage 1)** Livingston 2015 | 179 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,7,9 due to risk of bias, imprecision, publication bias | **RR 2.72**  (0.76 to 9.81) | **35 per 1000** | **60 more per 1000** (from 8 fewer to 307 more) |
| **Dobutamine vs. dopamine** Osborn 2007 | 42 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,7 due to imprecision, publication bias | **RR 2.73**  (0.31 to 24.14) | **50 per 1000** | **87 more per 1000** (from 34 fewer to 1000 more) |
| **Omega-3 in reducing the incidence of preterm birth** Saccone 2015 | 361 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 2.98**  (0.12 to 73.13) |  | **-** |
| **Intratracheal Clara cell secretory protein administration（1.5mg/kg）** Abdel-Latif 2011 | 15 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 4.44**  (0.25 to 79.42) |  | **-** |
| **Intratracheal Clara cell secretory protein administration（5mg/kg)** Abdel-Latif 2011 | 14 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RR 3.0**  (0.14 to 63.15) |  | **-** |
| **Early volume expansions (Gelatin vs. fresh frozen plasma)** Osborn 2004 | 518 (1 study) | ⊕⊝⊝⊝ **VERY LOW**1,3,5 due to risk of bias, imprecision, publication bias | **RR 4.92**  (1.44 to 16.8) | **12 per 1000** | **46 more per 1000** (from 5 more to 184 more) |
| **Interventionist versus expectant care (Interventionist care vs. expectant (delayed delivery) care)** Churchill 2002 | 133 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,6,7 due to risk of bias, imprecision, publication bias | **RR 5.54**  (1.04 to 29.56) | **15 per 1000** | **68 more per 1000** (from 1 more to 426 more) |
| **Partial exchange transfusion** Dempsey 2006 | 142 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,7,8 due to risk of bias, imprecision, publication bias | **RR 8.68**  (1.06 to 71.1) |  | **-** |
| **Planned early delivery vs. expectant management** Bond 2015 | 333 (1 study) | ⊕⊝⊝⊝ **VERY LOW**3,28 due to imprecision, publication bias | Not estimable | Not estimable | Not estimable |
| **Higher vs. lower protein intake in formula-fed infants** Fenton 2014 | 46 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**3,5,9 due to risk of bias, imprecision, publication bias | **RD 0**  (-0.12 to 0.12) | **45 per 1000** | **45 fewer per 1000** (from 40 fewer to 51 fewer) |
| \*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  **CI:** Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; | | | | | |
| GRADE Working Group grades of evidence **High certainty:** Further research is very unlikely to change our confidence in the estimate of effect.  **Moderate certainty:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low certainty:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low certainty:** We are very uncertain about the estimate. | | | | | |
| 1 Blinding of the healthcare provider and blinding of outcome assessment unclear 2 I2 is more than 50% 3 Less than 10 trials 4 Total number is more than 300, and with significant effect 5 Wide confidence interval 6 No allocation concealment 7 Sample size is very small 8 Randomization is not clear 9 Blinding is a problem 10 Allocation concealment is a problem 11 Selectiong report is a problem 12 Post allocation, drop out is a problem 13 Small sample size  14 Method of randomization is not clear 15 Treatment group allocation not blinded 16 Surrogate outcome close in the causal pathway to patient-important outcomes 17 Incomplete outcome data 18 Most of the studies lacked methodological details so that we were unable to judge risk of bias. This could have an impact on assessment of growth parameters and possibly the estimate of effect. 19 Few patients, few events and very wide conf idence intervals. 20 No explanation was provided 21 Intervention unblinded. 22 risk for bias because of allocation concealment and blinding 23 Data from a single study 24 All studies were at high risk of bias 25 Incomplete outcome data; High rate of noncompliance; Unclear allocation concealment 26 Unexplained heterogeneity and funnel plot asymmetry 27 Methodological limitations in included trials,  28Few total events (< 30). Wide CI crossing line of no effect and RR > 25%. | | | | | |

**eTable 6. GRADE Assessment of Intervention for Preventing Surgical NEC**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **No of Participants (studies)** Follow up | **Certainty of the evidence** (GRADE) | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
|  | |
| **Risk with Control** | **Risk difference with Surgical NEC** (95% CI) |
| **Oxygen Saturation Target Levels Lower (85%-89%) vs higher (91%-95%) SpO2** Askie 2018 | 4929 (5 studies) | ⊕⊕⊕⊝ **MODERATE**1 due to publication bias | **RR 1.33**  (1.1 to 1.61) | **69 per 1000** | **23 more per 1000** (from 7 more to 42 more) |
| **Arginine supplementation**  Shah 2017 | 285 (3 studies) | ⊕⊕⊝⊝ **LOW**1,2,3 due to imprecision, publication bias | **RR 0.13**  (0.02 to 1.03) | **55 per 1000** | **48 fewer per 1000** (from 54 fewer to 2 more) |
| **Donor-banked milk vs formula** Silano 2018 | 953 (4 studies) | ⊕⊕⊝⊝ **LOW**1,2 due to imprecision, publication bias | **RR 0.45**  (0.19 to 1.09) | **52 per 1000** | **28 fewer per 1000** (from 42 fewer to 5 more) |
| **Probiotics (Any)** Rees 2017 | 3975 (12 studies) | ⊕⊕⊝⊝ **LOW**2,4 due to risk of bias, imprecision | **RR 0.74**  (0.51 to 1.05) | **37 per 1000** | **10 fewer per 1000** (from 18 fewer to 2 more) |
| **Antistaphylococcal immunoglobulins to prevent staphylococcal infection** Shah 2009 | 2488 (2 studies) | ⊕⊕⊝⊝ **LOW**1,2 due to imprecision, publication bias | **RR 0.80**  (0.46 to 1.4) | **21 per 1000** | **4 fewer per 1000** (from 11 fewer to 8 more) |
| **N-acetylcysteine supplementation in parenterally fed neonates** Soghier 2006 | 391 (1 study) | ⊕⊕⊝⊝ **LOW**1,2 due to imprecision, publication bias | **RR 1.08**  (0.56 to 2.07) | **81 per 1000** | **6 more per 1000** (from 36 fewer to 87 more) |
| **Human milk feeding (Exclusive human milk vs. exclusive preterm formula)**  Miller 2018 | 53 (1 study) | ⊕⊝⊝⊝ **VERY LOW**1,5 due to imprecision, publication bias | **RR 0.09**  (0.01 to 1.64) | **167 per 1000** | **152 fewer per 1000** (from 165 fewer to 107 more) |
| **Human milk feeding (Unpasteurised vs. pasteurized human milk)** Miller 2018 | 303 (1 study) | ⊕⊝⊝⊝ **VERY LOW**1,5 due to imprecision, publication bias | **RR 0.11**  (0.01 to 2.06) | **26 per 1000** | **23 fewer per 1000** (from 26 fewer to 28 more) |
| **Oral immunoglobulin** Foster 2016 | 311 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**1,2,6 due to risk of bias, imprecision, publication bias | **RR 0.21**  (0.02 to 1.75) | **25 per 1000** | **20 fewer per 1000** (from 25 fewer to 19 more) |
| **Human milk feeding (Higher vs. lower dose human milk)**  Miller 2018 | 303 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**1,2,7 due to inconsistency, imprecision, publication bias | **RR 0.36**  (0.06 to 2.04) | **26 per 1000** | **17 fewer per 1000** (from 25 fewer to 27 more) |
| \*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  **CI:** Confidence interval; **RR:** Risk ratio; | | | | | |
| GRADE Working Group grades of evidence **High certainty:** Further research is very unlikely to change our confidence in the estimate of effect.  **Moderate certainty:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low certainty:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low certainty:** We are very uncertain about the estimate. | | | | | |
| 1 Less than 10 trials 2 Wide confidential interval 3 Small sample size. 4 Blinding is a problem. 5 Single study, wide confidential interval  6 Incomplete outcome data. Unclear allocation concealment. 7 Moderate heterogeneity | | | | | |

**eTable 7. GRADE Assessment of Intervention for ‘All-Cause Mortality’ During Hospital Stay**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **No of Participants (studies)** Follow up | **Certainty of the evidence** (GRADE) | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
|  | |
| **Risk with Control** | **Risk difference with Intervention** (95% CI) |
| **Probiotics (A combination of species)** Sawh 2016 | 4650 (18 studies) | ⊕⊕⊕⊝ **MODERATE**1 due to risk of bias | **RR 0.41**  (0.29 to 0.56) | **58 per 1000** | **34 fewer per 1000** (from 26 fewer to 41 fewer) |
| **Probiotics (Any)** Sawh 2016 | 9507 (29 studies) | ⊕⊕⊕⊝ **MODERATE**1 due to risk of bias | **RR 0.79**  (0.68 to 0.93) | **72 per 1000** | **15 fewer per 1000** (from 5 fewer to 23 fewer) |
| **Probiotics (Lactobacillus)** Sawh 2016 | 2596 (8 studies) | ⊕⊕⊝⊝ **LOW**1,2 due to risk of bias, publication bias | **RR 0.61**  (0.4 to 0.95) | **41 per 1000** | **16 fewer per 1000** (from 2 fewer to 25 fewer) |
| **Arginine supplementation** Shah 2017 (by original review author) | 285 (3 studies) | ⊕⊕⊝⊝ **LOW**2,3,4 due to imprecision, publication bias | **RR 0.77**  (0.41 to 1.45) | **124 per 1000** | **29 fewer per 1000** (from 73 fewer to 56 more) |
| **Antibiotics for preterm rupture of membranes Any antibiotic vs. placebo** Kenyon 2013 | 6301 (12 studies) | ⊕⊕⊝⊝ **LOW**1,5 due to risk of bias, imprecision | **RR 0.93**  (0.76 to 1.14) | **69 per 1000** | **5 fewer per 1000** (from 17 fewer to 10 more) |
| **Probiotics (Bifidobacterium)** Sawh 2016 | 2056 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**1,2,6 due to risk of bias, inconsistency, publication bias | **RR 0.37**  (0.14 to 0.97) | **100 per 1000** | **63 fewer per 1000** (from 3 fewer to 86 fewer) |
| **Lactoferrin plus probiotics vs. placebo** Pammi 2017 | 496 (1 study) | ⊕⊝⊝⊝ **VERY LOW**2,7,8 due to risk of bias, imprecision, publication bias | **RR 0.54**  (0.25 to 1.18) | **70 per 1000** | **32 fewer per 1000** (from 52 fewer to 13 more) |
| **Early trophic feeding vs. enteral fasting** Morgan 2013 | 558 (8 studies) | ⊕⊝⊝⊝ **VERY LOW**1,2,5,9 due to risk of bias, imprecision, publication bias | **RR 0.66**  (0.41 to 1.07) | **132 per 1000** | **45 fewer per 1000** (from 78 fewer to 9 more) |
| **Enteral antibiotics**  Bury 2001 | 215 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**2,5,9,10 due to risk of bias, imprecision, publication bias | **RR 0.67**  (0.34 to 1.32) | **165 per 1000** | **54 fewer per 1000** (from 109 fewer to 53 more) |
| **Antibiotics for preterm rupture of membranes [Antibiotics vs. no antibiotic (no placebo)]** Kenyon 2013 | 571 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**1,2,5 due to risk of bias, imprecision, publication bias | **RR 0.69**  (0.41 to 1.14) | **121 per 1000** | **37 fewer per 1000** (from 71 fewer to 17 more) |
| **Omega-3 long-chain polyunsaturated fatty acids** Zhang 2014 | 3749 (6 studies) | ⊕⊝⊝⊝ **VERY LOW**1,2,5 due to risk of bias, imprecision, publication bias | **RR 0.76**  (0.42 to 1.38) | **14 per 1000** | **3 fewer per 1000** (from 8 fewer to 5 more) |
| **Probiotics (Saccharomyces boulardii)** Sawh 2016 | 357 (2 studies) | ⊕⊝⊝⊝ **VERY LOW**1,2,5 due to risk of bias, imprecision, publication bias | **RR 0.72**  (0.33 to 1.54) | **76 per 1000** | **21 fewer per 1000** (from 51 fewer to 41 more) |
| **Colostrum**  Sadeghirad 2018 | 330 (7 studies) | ⊕⊝⊝⊝ **VERY LOW**2,11,12 due to risk of bias, imprecision, publication bias | **RR 0.84**  (0.39 to 1.82) | **74 per 1000** | **12 fewer per 1000** (from 45 fewer to 61 more) |
| **Prophylactic surgical ligation of PDA** Mosalli 2009 | 84 (1 study) | ⊕⊝⊝⊝ **VERY LOW**1,2,5 due to risk of bias, imprecision, publication bias | **RR 0.88**  (0.53 to 1.45) | **455 per 1000** | **55 fewer per 1000** (from 214 fewer to 205 more) |
| **Lactoferrin vs. placebo** Pammi 2017 | 5086 (10 studies) | ⊕⊝⊝⊝ **VERY LOW**2,6,7,13 due to risk of bias, imprecision, publication bias | **RR 0.94**  (0.75 to 1.19) | **53 per 1000** | **3 fewer per 1000** (from 13 fewer to 10 more) |
| **Slow (up to 24 mL/kg/d) vs. faster rates of advancement** Oddie 2017 | 3576 (9 studies) | ⊕⊝⊝⊝ **VERY LOW**2,5,14 due to risk of bias, imprecision, publication bias | **RR 1.15**  (0.93 to 1.42) | **71 per 1000** | **11 more per 1000** (from 5 fewer to 30 more) |
| **Delayed (≥4d) versus early introduction of progressive enteral feeding (24 mL/kg/** Morgan 2014 | 967 (7 studies) | ⊕⊝⊝⊝ **VERY LOW**1,2,5 due to risk of bias, imprecision, publication bias | **RR 1.18**  (0.75 to 1.88) | **58 per 1000** | **10 more per 1000** (from 14 fewer to 51 more) |
| **Red blood cell transfusions liberal (greater volume and/or number of RBC transfusions) versus restrictive transfusion practice** Keir 2016 | 951 (8 studies) | ⊕⊝⊝⊝ **VERY LOW**1,2,5 due to risk of bias, imprecision, publication bias | **RR 1.24**  (0.89 to 1.672) | **111 per 1000** | **27 more per 1000** (from 12 fewer to 75 more) |
| **Glycerin enemas and suppositories** Livingston 2015 | 179 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**2,5,10 due to risk of bias, imprecision, publication bias | **RR 1.34**  (0.58 to 3.11) | **93 per 1000** | **32 more per 1000** (from 39 fewer to 196 more) |
| **Dobutamine vs. dopamine**  Osborn 2007 | 42 (1 study) | ⊕⊝⊝⊝ **VERY LOW**2,4,5 due to imprecision, publication bias | **RR 1.41**  (0.79 to 2.52) | **450 per 1000** | **184 more per 1000** (from 94 fewer to 684 more) |
| **Adjunctive antibiotic treatment in preterm labor** Egarter 1996 | 549 (4 studies) | ⊕⊝⊝⊝ **VERY LOW**2,5,9,10 due to risk of bias, imprecision, publication bias | **OR 3.25**  (0.93 to 11.38) | **7 per 1000** | **16 more per 1000** (from 1 fewer to 69 more) |
| \*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  **CI:** Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; | | | | | |
| GRADE Working Group grades of evidence **High certainty:** Further research is very unlikely to change our confidence in the estimate of effect.  **Moderate certainty:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low certainty:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low certainty:** We are very uncertain about the estimate. | | | | | |
| 1 Blinding of intervention and outcome assessment is problem 2 Less than 10 trials 3 Minor sources of indirectness included (1) age and weight of included neonates (< 32 weeks and < 1250 grams vs < 34 weeks and < 1500 grams); (2) placebo composition (saline vs 5% glucose vs no treatment). These were not deemed by review authors to warrant downgrading of recommendations. 4 Small sample size 5 Wide confidence interval 6 Moderate or severe heterogeneity (I2 > 50% ) 7 Blinding of the healthcare provider and blinding of outcome assessment unclear 8 Data from a single study 9 Allocation of concealment is a problem 10 Blinding is a problem 11 risk for bias because of allocation concealment and blinding,  12 The 95% CI includes values suggesting substantial benefit and values suggesting substantial harm 13 Methods of randomization and allocation concealment are not available for 1 study 14 All trials unblinded | | | | | |

**eTable 8. GRADE Assessment of Intervention for NEC-Related Mortality**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **No of Participants (studies)** Follow up | **Certainty of the evidence** (GRADE) | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
|  | |
| **Risk with Control** | **Risk difference with** (95% CI) |
| **Arginine supplementation** Shah 2017 | 285 (3 studies) | ⊕⊕⊝⊝ **LOW**1,2 due to imprecision, publication bias | **RR 0.18**  (0.03 to 1) | **55 per 1000** | **45 fewer per 1000** (from 54 fewer to 0 more) |
| **Probiotics (Any)** Rees 2017 | Wrong number provided (13 studies) | ⊕⊕⊝⊝ **LOW**3,4 due to risk of bias, publication bias | **RR 0.56**  (0.34 to 0.93) | **1000 per 1000** | **440 fewer per 1000** (from 70 fewer to 660 fewer) |
| **Enteral antibiotics (aminoglycoside)** Bury 2001 | 257 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**2,3,5,6 due to risk of bias, imprecision, publication bias | **RR 0.32**  (0.1 to 0.96) | **92 per 1000** | **62 fewer per 1000** (from 4 fewer to 82 fewer) |
| **Oral immunoglobulin** Foster 2016 | 1840 (3 studies) | ⊕⊝⊝⊝ **VERY LOW**1,2,7 due to risk of bias, imprecision, publication bias | **RR 1.1**  (0.47 to 2.59) | **10 per 1000** | **1 more per 1000** (from 5 fewer to 16 more) |
| \*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  **CI:** Confidence interval; **RR:** Risk ratio; | | | | | |
| GRADE Working Group grades of evidence **High certainty:** Further research is very unlikely to change our confidence in the estimate of effect.  **Moderate certainty:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low certainty:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low certainty:** We are very uncertain about the estimate. | | | | | |
| 1 Wild confidence interval 2 Less than 10 trials 3 Blinding of intervention is a problem 4 Funnel plot is asymmetrical 5 Allocation concealment is a problem 6 Sample size is small 7 Incomplete outcome data.High rate of non-compliance.Unclear allocation concealment. | | | | | |

**eTable 9. Summary of Fingdings**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **NEC (Stage II or above; any stage)** | **Surgical NEC** | **‘All-cause mortality’ of infants during hospital stay** | **NEC-related mortality** |
| **Effective interventions  (*high-certainty evidence showing benefits*)** | None | None | None | None |
| **Possibly effective interventions  (*moderate-certainty evidence showing benefits*)** | 1. Probiotics (A combination of secies) | None | 1. Probiotics (A combination of secies) | None |
| 2. Antenatal corticosteroids for accelerating fetal lung maturation | 2. Probiotics (Any) |
| 3. Probiotics (Any) |  |
| 4. Ibuprofen vs. indomethacin for the treatment of PDA |  |
| **Ineffective interventions  (*high-certainty evidence with lack of benefit*)** | None | None | None | None |
| **Probably ineffective interventions *(moderate-certainty evidence with lack of benefit)*** | **A. Harm effect** | **A. Harm effect** | None | None |
| None | Lower (85%-89%) vs. higher (91%-95%) oxygen saturation target levels |
| **B. Lack of effectiveness** | **B. Lack of effectiveness** |
| 1. Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease | None |
| 2. Early erythropoietin for preventing red blood cell transfusion |  |
| 3. Prophylactic intravenous indomethacin |  |
| **No conclusions possible  *(low- or very low-certainty evidence)*** | See eFigures 2-3 | 1. Arginine supplementation  2. Donor-banked milk vs. Formula  3. Probiotics (Any)  4. Anti-staphylococcal immunoglobulins to prevent staphylococcal infection  5. N-acetylcysteine supplementation in parenterally fed neonates  6. Exclusive human milk vs. Exclusive preterm formula  7. Unpasteurized vs. pasteurized human milk  8. Oral immunoglobulin  9. Higher vs. Lower dose human milk | 1. Probiotics (Lactobacillus)  2. Arginine supplementation  3. Antibiotics for preterm rupture of membranes (Antibiotic vs. placebo)  4. Probiotics (Bifidobacterium)  5. Lactoferrin plus probiotics vs. placebo  6. Early trophic feeding vs. enteral fasting  7. Enteral antibiotics  8. Antibiotics for preterm rupture of membranes (Antibiotics vs.no placebo)  9. Probiotics (Saccharomyces boulardii)  10. Omega-3 long-chain polyunsaturated fatty acids  11. Colostrum  12. Prophylactic surgical ligation of PDA  13. Lactoferrin vs. Placebo  14. Slow (up to 24 ml/kg/d) vs. faster rates of advancement of enteral feed volumes  15. Delayed (≥4d) vs. early introduction of progressive enteral feeding (24 ml/kg/day)  16. Red blood cell transfusions (Liberal vs. restrictive transfusion)  17. Glycerin enemas and suppositories  18. Dobutamine vs. dopamine  19. Adjunctive antibiotic treatment in preterm labor | 1. Arginine supplementation  2. Probiotics (Any)  3. Enteral antibiotics (Aminoglycoside)  4. Oral immunoglobulin |

**References to included reviews**

1 Roberts D, Brown J, Medley N, Dalziel SR: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. The Cochrane database of systematic reviews 2017Mar 21;3CD004454.

2 Flenady V, Reinebrant HE, Liley HG, Tambimuttu EG, Papatsonis DN: Oxytocin receptor antagonists for inhibiting preterm labour. The Cochrane database of systematic reviews 2014Jun 6;(6):Cd004452.

3 Flenady V, Wojcieszek AM, Papatsonis DNM, Stock OM, Murray L, Jardine LA, et al.: Calcium channel blockers for inhibiting preterm labour and birth. Cochrane Database of Systematic Reviews 20142014(6):

4 Dodd JM, Jones L, Flenady V, Crowther CA: Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Cochrane Database of Systematic Reviews 20132013(7):

5 Bond Diana M, Middleton P, Levett Kate M, van der Ham David P, Crowther Caroline A, Buchanan Sarah L, et al.: Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD004735.pub4.

6 Watson J, McGuire W: Transpyloric versus gastric tube feeding for preterm infants. The Cochrane database of systematic reviews 2013Feb 28;(2):CD003487.

7 Kenyon S, Boulvain M, Neilson JP: Antibiotics for preterm rupture of membranes. The Cochrane database of systematic reviews 2013Dec 2;(12):CD001058.

8 Sadeghirad B, Morgan RL, Zeraatkar D, Zea AM, Couban R, Johnston BC, et al.: Human and Bovine Colostrum for Prevention of Necrotizing Enterocolitis: A Meta-analysis. Pediatrics 2018Jul 10;142(2):e20180767.

9 Oddie SJ, Young L, McGuire W: Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. The Cochrane database of systematic reviews 2017Aug 30;8CD001241.

10 Zhang P, Lavoie PM, Lacaze-Masmonteil T, Rhainds M, Marc I: Omega-3 long-chain polyunsaturated fatty acids for extremely preterm infants: A systematic review. Pediatrics 2014134(1):120-134.

11 Stock SJ, Bricker L, Norman JE, West HM: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes. The Cochrane database of systematic reviews 2016Jul 12;7CD008968.

12 Saccone G, Berghella V: Omega-3 long chain polyunsaturated fatty acids to prevent preterm birth: a systematic review and meta-analysis. Obstetrics and gynecology 2015Mar;125(3):663-672.

13 Bond DM, Gordon A, Hyett J, de Vries B, Carberry AE, Morris J: Planned early delivery versus expectant management of the term suspected compromised baby for improving outcomes. Cochrane Database of Systematic Reviews 20152015(11):

14 Neilson JP, West HM, Dowswell T: Betamimetics for inhibiting preterm labour. The Cochrane database of systematic reviews 2014Feb 5;(2):CD004352.

15 Flenady V, Hawley G, Stock Owen M, Kenyon S, Badawi N: Prophylactic antibiotics for inhibiting preterm labour with intact membranes. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD000246.pub2.

16 Woudstra DM, Chandra S, Hofmeyr GJ, Dowswell T: Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy. The Cochrane database of systematic reviews 2010Sep 8;(9):Cd008148.

17 Lemyre B, Davis PG, De Paoli AG, Kirpalani H: Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. Cochrane Database of Systematic Reviews 20172017(2):

18 Hyttel-Sorensen S, Greisen G, Als-Nielsen B, Gluud C: Cerebral near-infrared spectroscopy monitoring for prevention of brain injury in very preterm infants. The Cochrane database of systematic reviews 2017Sep 4;9CD011506.

19 Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL: Late (> 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database of Systematic Reviews 20172017(10):

20 Moe-Byrne T, Brown JV, McGuire W: Glutamine supplementation to prevent morbidity and mortality in preterm infants. The Cochrane database of systematic reviews 2016Jan 12;(1):CD001457.

21 Shah Sachin S, Ohlsson A, Halliday Henry L, Shah Vibhuti S: Inhaled versus systemic corticosteroids for the treatment of bronchopulmonary dysplasia in ventilated very low birth weight preterm infants. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD002057.pub4.

22 Oei JL, Vento M, Rabi Y, Wright I, Finer N, Rich W, et al.: Higher or lower oxygen for delivery room resuscitation of preterm infants below 28 completed weeks gestation: a meta-analysis. Archives of disease in childhood Fetal and neonatal edition 2017Jan;102(1):F24-F30.

23 Osborn DA, Schindler T, Jones LJ, Sinn JKH, Bolisetty S: Higher versus lower amino acid intake in parenteral nutrition for newborn infants. Cochrane Database of Systematic Reviews 20182018(3):

24 Ohlsson A, Aher SM: Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. The Cochrane database of systematic reviews 2014Apr 26;(4):CD004863.

25 Doyle LW, Ehrenkranz RA, Halliday HL: Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. The Cochrane database of systematic reviews 2014May 13;(5):CD001146.

26 Aher SM, Ohlsson A: Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. The Cochrane database of systematic reviews 2014Apr 23;(4):CD004868.

27 Ohlsson A, Lacy Janet B: Intravenous immunoglobulin for preventing infection in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD000361.pub3.

28 Osborn DA, Hunt RW: Postnatal thyroid hormones for respiratory distress syndrome in preterm infants. The Cochrane database of systematic reviews 2007Jan 24;(1):CD005946.

29 Ohlsson A, Walia R, Shah Sachin S: Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD003481.pub6.

30 Sawh SC, Deshpande S, Jansen S, Reynaert CJ, Jones PM: Prevention of necrotizing enterocolitis with probiotics: A systematic review and meta-analysis. PeerJ 20162016(10):

31 Shah PS, Shah VS, Kelly LE: Arginine supplementation for prevention of necrotising enterocolitis in preterm infants. Cochrane Database of Systematic Reviews 20172017(4):

32 Pammi M, Suresh G: Enteral lactoferrin supplementation for prevention of sepsis and necrotizing enterocolitis in preterm infants. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD007137.pub5.

33 Bury RG, Tudehope D: Enteral antibiotics for preventing necrotizing enterocolitis in low birthweight or preterm infants. Cochrane database of systematic reviews (Online) 2001(1):CD000405.

34 Churchill D, Duley L: Interventionist versus expectant care for severe pre-eclampsia before term. The Cochrane database of systematic reviews 2002(3):CD003106.

35 Quigley M, Embleton Nicholas D, McGuire W: Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD002971.pub4.

36 Morgan J, Young L, McGuire W: Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. The Cochrane database of systematic reviews 2014(12):CD001970.

37 Morgan J, Bombell S, McGuire W: Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants. The Cochrane database of systematic reviews 2013Mar 28;(3):CD000504.

38 Foster JP, Seth R, Cole MJ: Oral immunoglobulin for preventing necrotizing enterocolitis in preterm and low birth weight neonates. The Cochrane database of systematic reviews 2016Apr 4;4CD001816.

39 Premji SS, Chessell L: Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. The Cochrane database of systematic reviews 2011Nov 9;(11):CD001819.

40 Livingston MH, Shawyer AC, Rosenbaum PL, Williams C, Jones SA, Walton JM: Glycerin enemas and suppositories in premature infants: a meta-analysis. Pediatrics 2015Jun;135(6):1093-1106.

41 Osborn DA, Paradisis M, Evans N: The effect of inotropes on morbidity and mortality in preterm infants with low systemic or organ blood flow. The Cochrane database of systematic reviews 2007Jan 24;(1):CD005090.

42 van Vliet E, Dijkema GH, Schuit E, Heida KY, Roos C, van der Post J, et al.: Nifedipine maintenance tocolysis and perinatal outcome: an individual participant data meta-analysis. BJOG : an international journal of obstetrics and gynaecology 2016Oct;123(11):1753-1760.

43 Saccone G, Suhag A, Berghella V: 17-alpha-hydroxyprogesterone caproate for maintenance tocolysis: a systematic review and metaanalysis of randomized trials. American Journal of Obstetrics and Gynecology 2015213(1):16-22.

44 Deshmukh M, Balasubramanian H, Patole S: Meconium evacuation for facilitating feed tolerance in preterm neonates: A systematic review and meta-analysis. Neonatology 2016110(1):55-65.

45 Brown Jennifer VE, Embleton Nicholas D, Harding Jane E, McGuire W: Multi-nutrient fortification of human milk for preterm infants. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD000343.pub3.

46 Kapoor V, Glover R, Malviya Manoj N: Alternative lipid emulsions versus pure soy oil based lipid emulsions for parenterally fed preterm infants. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD009172.pub2.

47 Foster JP, Richards R, Showell MG, Jones LJ: Intravenous in-line filters for preventing morbidity and mortality in neonates. The Cochrane database of systematic reviews 2015Aug 6;(8):CD005248.

48 Fenton TR, Premji SS, Al-Wassia H, Sauve RS: Higher versus lower protein intake in formula-fed low birth weight infants. Cochrane Database of Systematic Reviews 20142014(4):

49 Ng G, Ohlsson A: Cromolyn sodium for the prevention of chronic lung disease in preterm infants. The Cochrane database of systematic reviews 2017Jan 23;1CD003059.

50 Ng DHC, Klassen J, Embleton ND, McGuire W: Protein hydrolysate versus standard formula for preterm infants. The Cochrane database of systematic reviews 2017Oct 2;10Cd012412.

51 Lui K, Jones Lisa J, Foster Jann P, Davis Peter G, Ching See K, Oei Ju L, et al.: Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD010239.pub2.

52 Fogarty M, Osborn DA, Askie L, Seidler AL, Hunter K, Lui K, et al.: Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. American journal of obstetrics and gynecology 2018Jan;218(1):1-18.

53 Amissah EA, Brown J, Harding JE: Protein supplementation of human milk for promoting growth in preterm infants. Cochrane Database of Systematic Reviews 20182018(6):

54 Tan-Dy CRY, Ohlsson A: Lactase treated feeds to promote growth and feeding tolerance in preterm infants. Cochrane Database of Systematic Reviews 20132013(3):

55 Malviya MN, Ohlsson A, Shah SS: Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants. The Cochrane database of systematic reviews 2013Mar 28;(3):CD003951.

56 Howlett A, Ohlsson A, Plakkal N: Inositol for respiratory distress syndrome in preterm infants. The Cochrane database of systematic reviews 2012Mar 14;(3):CD000366.

57 Bottino M, Cowett Richard M, Sinclair John C: Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD007453.pub3.

58 Abdel-Latif ME, Osborn DA: Intratracheal Clara cell secretory protein (CCSP) administration in preterm infants with or at risk of respiratory distress syndrome. The Cochrane database of systematic reviews 2011May 11;(5):CD008308.

59 Soll R, Özek E: Prophylactic protein free synthetic surfactant for preventing morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD001079.pub2.

60 Shah PS, Kaufman DA: Antistaphylococcal immunoglobulins to prevent staphylococcal infection in very low birth weight infants. The Cochrane database of systematic reviews 2009Apr 15;(2):CD006449.

61 Ng E, Shah Vibhuti S: Erythromycin for the prevention and treatment of feeding intolerance in preterm infants. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD001815.pub2.

62 Fowlie Peter W, Davis Peter G, McGuire W: Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD000174.pub2.

63 Osborn DA, Hunt RW: Postnatal thyroid hormones for preterm infants with transient hypothyroxinaemia. The Cochrane database of systematic reviews 2007Jan 24;(1):CD005945.

64 Soghier LM, Brion LP: Cysteine, cystine or N-acetylcysteine supplementation in parenterally fed neonates. The Cochrane database of systematic reviews 2006Oct 18;(4):CD004869.

65 Simmer K, Rao Shripada C: Early introduction of lipids to parenterally-fed preterm infants. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD005256.

66 Kabra NS, Kumar M, Shah SS: Multiple versus single lumen umbilical venous catheters for newborn infants. The Cochrane database of systematic reviews 2005Jul 20;(3):CD004498.

67 Jardine LA, Jenkins-Manning S, Davies MW: Albumin infusion for low serum albumin in preterm newborn infants. The Cochrane database of systematic reviews 2004(3):CD004208.

68 Barrington KJ: Umbilical artery catheters in the newborn: effects of position of the catheter tip. The Cochrane database of systematic reviews 2000(2):CD000505.

69 Pfister RH, Soll RF, Wiswell T: Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome. The Cochrane database of systematic reviews 2007Jul 18;(3):CD006069.

70 Osborn DA, Evans N: Early volume expansion for prevention of morbidity and mortality in very preterm infants. The Cochrane database of systematic reviews 2004(2):CD002055.

71 Rees CM, Hall NJ, Fleming P, Eaton S: Probiotics for the prevention of surgical necrotising enterocolitis: systematic review and meta-analysis. BMJ paediatrics open 20171(1):e000066.

72 Miller J, Tonkin E, Damarell RA, McPhee AJ, Suganuma M, Suganuma H, et al.: A systematic review and meta-analysis of human milk feeding and morbidity in very low birth weight infants. Nutrients 201810(6):

73 Mosalli R, Alfaleh K, Paes B: Role of prophylactic surgical ligation of patent ductus arteriosus in extremely low birth weight infants: Systematic review and implications for clinical practice. Annals of Pediatric Cardiology 20092(2):120-126.

74 Conde-Agudelo A, Romero R, Kusanovic JP: Nifedipine in the management of preterm labor: a systematic review and metaanalysis. American journal of obstetrics and gynecology 2011Feb;204(2):134 e131-120.

75 Ardell S, Pfister RH, Soll R: Animal derived surfactant extract versus protein free synthetic surfactant for the prevention and treatment of respiratory distress syndrome. The Cochrane database of systematic reviews 2015Aug 24;8CD000144.

76 Silano M, Milani GP, Fattore G, Agostoni C: Donor human milk and risk of surgical necrotizing enterocolitis: A meta-analysis. Clinical Nutrition 2018

77 Saccone G, Berghella V: Omega-3 supplementation to prevent recurrent preterm birth: A systematic review and metaanalysis of randomized controlled trials. American Journal of Obstetrics and Gynecology 2015213(2):135-140.

78 Wu W, Shi Y, Li F, Wen Z, Liu H: Surfactant administration via a thin endotracheal catheter during spontaneous breathing in preterm infants. Pediatric pulmonology 2017Jun;52(6):844-854.

79 Vayalthrikkovil S, Bashir RA, Rabi Y, Amin H, Spence JM, Robertson HL, et al.: Parenteral Fish-Oil Lipid Emulsions in the Prevention of Severe Retinopathy of Prematurity: A Systematic Review and Meta-Analysis. American Journal of Perinatology 201734(7):705-715.

80 Fleeman N, Mahon J, Bates V, Dickson R, Dundar Y, Dwan K, et al.: The clinical effectiveness and cost-effectiveness of heated humidified high-flow nasal cannula compared with usual care for preterm infants: Systematic review and economic evaluation. Health Technology Assessment 201620(30):1-70.

81 Moyses HE, Johnson MJ, Leaf AA, Cornelius VR: Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis. The American journal of clinical nutrition 2013Apr;97(4):816-826.

82 Ibrahim M, Ho SK, Yeo CL: Restrictive versus liberal red blood cell transfusion thresholds in very low birth weight infants: a systematic review and meta-analysis. J Paediatr Child Health 2014Feb;50(2):122-130.

83 Henderson-Smart DJ, Subramaniam P, Davis PG: Continuous positive airway pressure versus theophylline for apnea in preterm infants. The Cochrane database of systematic reviews 2001(4):CD001072.

84 Bell EF, Acarregui MJ: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. The Cochrane database of systematic reviews 2014(12):CD000503.

85 Soll R, Ozek E: Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. The Cochrane database of systematic reviews 2009Jan 21;(1):CD000141.

86 Herrera C, Holberton J, Davis P: Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. The Cochrane database of systematic reviews 2007Apr 18;(2):CD003480.

87 Bahadue Felicia L, Soll R: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD001456.pub2.

88 Keir A, Pal S, Trivella M, Lieberman L, Callum J, Shehata N, et al.: Adverse effects of red blood cell transfusions in neonates: a systematic review and meta-analysis. Transfusion 201656(11):2773-2780.

89 Srinivasjois R, Rao S, Patole S: Prebiotic supplementation in preterm neonates: updated systematic review and meta-analysis of randomised controlled trials. Clinical nutrition (Edinburgh, Scotland) 2013Dec;32(6):958-965.

90 Boyd CA, Quigley MA, Brocklehurst P: Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis. Archives of disease in childhood Fetal and neonatal edition 2007May;92(3):F169-175.

91 Dempsey EM, Barrington K: Short and long term outcomes following partial exchange transfusion in the polycythaemic newborn: a systematic review. Archives of disease in childhood Fetal and neonatal edition 2006Jan;91(1):F2-6.

92 Smithers LG, Gibson RA, McPhee A, Makrides M: Effect of long-chain polyunsaturated fatty acid supplementation of preterm infants on disease risk and neurodevelopment: a systematic review of randomized controlled trials. The American journal of clinical nutrition 2008Apr;87(4):912-920.

93 Jin HX, Wang RS, Chen SJ, Wang AP, Liu XY: Early and late Iron supplementation for low birth weight infants: a meta-analysis. Italian journal of pediatrics 2015Mar 14;4116.

94 Huang X, Wang F, Wang K: Paracetamol versus ibuprofen for the treatment of patent ductus arteriosus in preterm neonates: a meta-analysis of randomized controlled trials. Journal of Maternal-Fetal and Neonatal Medicine 201831(16):2216-2222.

95 Hutzal CE, Boyle EM, Kenyon SL, Nash JV, Winsor S, Taylor DJ, et al.: Use of antibiotics for the treatment of preterm parturition and prevention of neonatal morbidity: a metaanalysis. American Journal of Obstetrics and Gynecology 2008199(6):620.e621-620.e628.

96 Askie LM, Darlow BA, Finer N, Schmidt B, Stenson B, Tarnow-Mordi W, et al.: Association Between Oxygen Saturation Targeting and Death or Disability in Extremely Preterm Infants in the Neonatal Oxygenation Prospective Meta-analysis Collaboration. Jama 2018Jun 5;319(21):2190-2201.

97 Egarter C, Leitich H, Husslein P, Kaider A, Schemper M: Adjunctive antibiotic treatment in preterm labor and neonatal morbidity: a meta-analysis. Obstetrics and gynecology 1996Aug;88(2):303-309.

98 Leitich H, Egarter C, Reisenberger K, Kaider A, Berghammer P: Concomitant use of glucocorticoids: a comparison of two metaanalyses on antibiotic treatment in preterm premature rupture of membranes. American journal of obstetrics and gynecology 1998May;178(5):899-908.