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| Question | |
| **NLS 5312- CPAP versus No CPAP for Term Respiratory Distress in Delivery Room** | |
| **Population:** | In spontaneously breathing newly born ≥34+0 weeks gestation infants with respiratory distress and/or low oxygen saturations during transition after birth. |
| **Intervention:** | Continuous positive airway pressure (CPAP) (at different levels with or without supplemental oxygen) |
| **Comparison:** | Compared with no CPAP (with or without supplemental oxygen) |
| **Main outcomes:** | Admissions to neonatal intensive care unit (NICU) or higher level of care receiving any positive pressure support [primary outcome]; receiving tracheal intubation or chest compressions in the delivery room; use and duration of respiratory support in NICU; air-leak syndromes including pneumothorax and pneumomediastinum; death at hospital discharge; length of hospital stay; moderate-severe neurodevelopmental impairment (>18 months) |
| **Setting:** | Delivery room |
| **Perspective:** |  |
| **Background:** |  |
| **Conflict of interests:** | None |

# Assessment

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| Problem Is the problem a priority? | | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | At birth, the newly born infant rapidly undergoes major and complex physiologic changes. Failure to establish and maintain air breathing from the fluid-filled environment of the womb leads to impaired transition. Resultant respiratory distress is common, affecting up to 7% of all term newborns (Edwards 2013 29), and is even more prevalent in late preterm infants. Further, respiratory distress is responsible for 30-40% of admissions to the neonatal intensive care units (NICU) (Guha DK, editor Neonatology - Principles and Practice, 1st ed. 1998). Fifteen percent of term infants and 29% of late preterm infants admitted to the NICU develop significant respiratory morbidity (Hibbard 2010 419).  The etiology of respiratory distress among term and late preterm newborn infants is heterogeneous and includes transient tachypnea of newborn, respiratory distress syndrome (surfactant deficiency), pneumonia, and meconium aspiration syndrome. These conditions present similarly in a non-specific manner, with signs such as tachypnea, nasal flaring, retractions, and grunting, making precise diagnosis difficult. Symptoms may progress to respiratory failure and death if not readily recognized and managed appropriately (Warren 2010 487). In infants with progressive respiratory failure, mechanical ventilation (MV) with or without surfactant has been the usual treatment. This approach is invasive and may contribute to airway and lung injury.  Therapy for respiratory distress traditionally consisted of oxygen given via headbox, low-flow nasal prong or cannula, or face mask. Continuous positive airway pressure (CPAP), a non-invasive form of respiratory support, has also been used for the prevention and treatment of respiratory distress. CPAP devices apply a positive pressure to the airways of a spontaneously breathing baby throughout the respiratory cycle. Extrapolated from evidence in preterm babies that CPAP applied early after birth improves survival without bronchopulmonary dysplasia (BPD) (Schmölzer 2013 f5980 and Subramaniam 2016 1465), there has been progressively increased use of CPAP among term and late preterm newly born infants (Smithhart 2019, Hishikawa 2016 1). |  |

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| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | In preterm infants less than 32 weeks, early CPAP use decreases the need for mechanical ventilation and decreases the risk of death or chronic lung disease (Subramaniam 2016 1465). The effect of CPAP applied in the delivery room in term and late preterm infants with respiratory distress has been less clear. In the literature search for the current review, two randomized controlled trials (RCTs) were available in this population. In these studies, the RR of NICU admission was 0.27 (0.11, 0.66) when CPAP was applied to infants delivered by cesarean section with or without respiratory distress. One RCT used CPAP as treatment for babies with respiratory distress; another RCT with a larger sample size used prophylactic CPAP. On average, 94/1000 fewer infants treated with CPAP in the delivery room (DR) were admitted to the NICU than infants not treated with CPAP. These RCTs were small (totaling 323 subjects) and included only infants delivered by cesarean section. Therefore, conclusions should be considered with caution. If the outcomes are confirmed in larger trials, the impact on infants in this population would be substantial. The magnitude of effect from the included trials leads to a number needed to treat of 10.8 with a 95% CI of 8.7 to 22.7; for every ~11 infants treated with CPAP, 1 fewer infant will be admitted to the NICU.  However, since the two RCTs included only newborns born by caesarean section, CPAP should be evaluated among vaginally delivered newborns in a randomized fashion. Of the two observational studies included in this systematic review, one studied only a cohort of NICU admissions and therefore cannot be evaluated for main outcome of NICU admission. The other before-after observational study with a larger sample that included vaginal and cesarean deliveries found the opposite effect on NICU admissions, when compared with RCTs. There was also a positive association between CPAP use and NICU admissions. To summarize, we cannot exclude benefit or harm for CPAP use in the delivery room due to the scarcity and heterogeneity of the available evidence. | In preterm infants, CPAP increases transpulmonary pressure and functional residual capacity (FRC) and improves lung compliance. It also prevents alveolar collapse (atelectrauma), decreases intrapulmonary shunt, and provides progressive alveolar recruitment. In addition, CPAP conserves surfactant and prevents pharyngeal wall collapse. It also stabilizes the chest wall and decreases thoracoabdominal asynchrony and work of breathing if there is respiratory distress (Elgellab 2001 1782). Moreover, it splints the diaphragm and stimulates lung growth (Zhang 1996 1471). Finally, bubble CPAP adds high-frequency ventilation (Lee 1998 69) and stochastic resonance effects (Pillow 2005 826). Hence, CPAP use may improve respiratory distress in the newborn and reduce the NICU admissions and the need for MV and hence its sequelae, including airway and lung injury. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know | The RCTs available for this review comparing 168 subjects with CPAP of 5 cm H2O versus 155 subjects with no CPAP reported no cases of pulmonary air leak, but they have a small sample size and one study used CPAP prophylactically. Two observational studies included in this review found a positive association between CPAP use and occurrence of air leak syndromes, including pneumothorax. The RR for pneumothorax/air leak in these infants was 4.92 (4.13, 5.87). These studies are limited by significant selection bias.  Similarly, CPAP use was associated with an increase in NICU respiratory support with the RR 7.78 (4.25, 14.24) and length of hospital stay with the MD 1 (0.31, 1.69) in a single-center observational cohort studying term newborn infants. However, NICU respiratory support was reported in two RCTs and length of hospital stay was reported in one RCT. No statistically significant differences were reported between newborns who received CPAP and those who did not receive CPAP in RCTs enrolling late preterm and term newborn infants born via cesarean deliveries. | CPAP may introduce ongoing risk during transition after birth and beyond (in NICU). In preterm human observational studies, apnea was seen after applying the interfaces used to provide CPAP. Hence, it is speculated that interfaces used to provide CPAP could stimulate the receptors of the trigeminal nerve and provoke the diving reflex, with resultant apnea and bradycardia (Kuypers 2020 60). Pulmonary air leak syndromes, including pneumothorax, may be more common with CPAP treatment and may require invasive interventions, such as thoracentesis or thoracostomy tube, and lead to further complications (Morley 2008 700). Higher levels of CPAP may lead to increased dead space ventilation and cause retention of carbon dioxide. Excessive CPAP can increase intrathoracic pressure, resulting in diminished venous return to the heart and reduced cardiac output, decreased pulmonary perfusion, and enhanced ventilation-perfusion mismatch. Gastric distension and decreased gastrointestinal blood flow may occur with the application of CPAP (Jaile 1992 125). Nasal obstruction from secretions or improper application of nasal prongs has been described (Wung 1975 76). The approach may cause local drying, cracking, irritation, or trauma, resulting in nasal septum erosion, necrosis, or deformities. If the infant breathes with the mouth widely open, it may lead to fluctuations in oxygenation. There may be a subgroup of as-yet-unidentified babies that may benefit from the CPAP and another subgroup in which the CPAP increases the risk of undesirable effects. Further investigations should address these questions. |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Very low ○ Low ○ Moderate ○ High ○ No included studies | Despite a large effect size with a robust confidence interval for the main outcome of NICU admission from two RCTs, the certainty of evidence was downgraded to low, recognizing serious risk of bias (not blinded), serious imprecision (small sample size), and serious indirectness (only cesarean deliveries; Celebi 2016 also included newborn infants without respiratory distress with prophylactic CPAP). Neither RCT specified the criteria for NICU admissions, thereby introducing risk for assessment bias. These RCTs found a statistically significant decrease in NICU respiratory support with CPAP when compared with no CPAP with a large magnitude of effect, which may be considered a proxy for a higher level of care.  The certainty of evidence is very low for the main outcome of NICU admission from one observational study (Hishikawa 2016), which is moderately limited by confounding, classification of interventions, deviations from intended interventions and missing data, and seriously limited by measurement of outcomes and overall bias.  The certainly of evidence was very low for the secondary outcome of pulmonary air leak from two RCTs, and low from two observational studies due to a strong positive association between CPAP and air leak syndromes.  The certainty of evidence ranged from low to very low for the secondary outcomes of length of hospital stay and death at hospital discharge. |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability | The group places value on both harm avoidance (increase in pulmonary air leak syndromes) and the potential benefit (decrease in NICU admissions and respiratory support) of CPAP with or without supplemental oxygen. Despite available studies that were considered to have a high risk of bias, and the certainty of evidence ranging from low to very low for the considered outcomes, the reduction in NICU admission is an outcome that would be valued by most stakeholders. Similarly, pneumothorax or air leak syndromes is an important outcome and if CPAP were confirmed to be causative in the pathogenesis of disease, avoidance of this outcome would be valued by most stakeholders. |  |

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| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know | There are discrepancies in the direction of effect in benefit versus harm among the RCTs and the observational studies included in this review. While we put slightly more value on the RCTs over the observational studies, the observational studies included a large number of subjects, which contributes to that overall uncertainty.  The RCTs reviewed suggest a benefit of CPAP after cesarean section in reducing NICU admission. One study applied CPAP to all babies, regardless of signs of respiratory distress. The other study included only babies with signs of respiratory distress. It is unknown whether this effect would be similar in infants delivered vaginally.  The observational studies identified a potential risk of pneumothorax. There is lack of precision in this finding, given that one study focused only on NICU admissions, and both compared populations inherently different from each other in that the decision to initiate CPAP was not based on a randomized approach. | It is important to consider that the balance of effects of using CPAP in the delivery room could be different depending on gestational age (late preterm vs term), mode of delivery (vaginal vs c-section), presence of labor before a c-section or if CPAP is used in symptomatic patients vs using it as prophylactic CPAP. |
| Resources required How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know | Although there are no published data on resource utilization, it is likely that CPAP use increases the cost of delivery room supplies.  CPAP may be provided in several ways, requiring different types of resources that have variable associated costs. Use of CPAP requires resources, including equipment and team training in the labor and delivery room. It may include gas sources, especially if oxygen is supplemented. These resources may already be in place in many settings.  Disposable costs will be increased if CPAP is recommended in all age groups. This may be challenging in some resource-limited settings. |  |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies | There were no studies that stated or reported the resources requirement, including costs, personnel, and infrastructure. |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies | No studies were found that compared the cost-effectiveness of use of CPAP vs. no CPAP for respiratory distress among term and late preterm infants. | Decreasing NICU admissions would likely decrease the overall cost of care, including length of stay, and have the potential for some savings, despite the increased cost associated with CPAP use.  There was a positive association between the CPAP use and air leaks from the observational data. The external validity of this weak evidence with low certainty data from single center remains purely speculative. If this speculation proves to be true in future RCTs, there may be increased costs in a subset of newborn infants (for example, babies born vaginally or without respiratory distress) with symptoms requiring intensive care monitoring, evaluation and management, including mechanical ventilation and/or needle or tube thoracentesis.  It may be worth performing cost-effectiveness analysis on putting resources into CPAP availability, which could lead to overall reduced costs. |

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| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know | No data available. | We speculate that equipment and adequately trained personnel to perform the intervention may not be always available, especially in low-resource settings. An intervention that does not include CPAP with or without supplemental oxygen may be more likely to increase health equity globally, including in low-resource settings.  The implementation of CPAP in low-resource settings may decrease NICU admissions, thereby making care more efficient and affordable. On the other hand, if the positive association between CPAP use and pneumothoraces found in the observational studies were to be true in randomized trials, CPAP use may reduce the health equity in a subset of symptomatic newborn infants who may be admitted to special care nursery and/or require invasive treatment. Caution should be exercised since we do not know how even a large observational data set from a high-resource single NICU setting would translate to populations in high- or low-resource settings, even within countries that generally have good resources. |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | CPAP is widely used internationally. It is likely to be accepted by stakeholders in settings where the resources are available. |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | From a practical point of view, CPAP is feasible, especially with t-piece resuscitator availability in labor and delivery rooms. CPAP may not be feasible where equipment is limited or unavailable. | In considering the feasibility to implement the use of CPAP, training of staff is very important. |

Summary of judgements

|  | **Judgement** | | | | | | |
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| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | **Large** |  | Varies | **Don't know** |
| **Undesirable Effects** | Large | Moderate | Small | Trivial |  | **Varies** | **Don't know** |
| **Certainty of evidence** | **Very low** | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | **No important uncertainty or variability** |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | **Varies** | Don't know |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | **Don't know** |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | **Probably reduced** | Probably no impact | Probably increased | Increased | Varies | **Don't know** |
| **Acceptability** | No | Probably no | **Probably yes** | **Yes** |  | **Varies** | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | **Yes** |  | **Varies** | Don't know |

**Type of recommendation**

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

# Conclusions

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| Recommendation |
| For spontaneously breathing late preterm and term newborn infants in the delivery room with respiratory distress, there is insufficient evidence to suggest for or against routine use of CPAP compared with no CPAP. |

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| Justification |
| In making this recommendation, the Neonatal Life Support Task Force acknowledges the following:   * The use of CPAP in the delivery room (DR) has been recommended for babies with persistent signs of respiratory distress, labored breathing, or cyanosis after the initial steps of resuscitation. This has been mainly extrapolated from evidence in preterm patients. The benefits and risks in late preterm and term babies had not previously been systematically reviewed. * The two RCTs included only 323 subjects, who were all delivered by cesarean section (one RCT enrolled 259 newborns used prophylactic CPAP). * Within the observational studies we identified a positive association between the use of CPAP and the presence of air leak syndromes (one nested cohort study included only babies admitted to the NICU). * Therefore, in making this recommendation, we integrate the values placed on avoidance of potential harm as noted by the positive association between CPAP use and air leak syndromes and potential benefit as noted by the reduction in NICU admission among infants born by cesarean section. |
| Subgroup considerations |
| For subgroup of spontaneously breathing late preterm and term infants born by cesarean section, use of CPAP may be considered compared with no CPAP to reduce the likelihood of NICU admission (weak conditional recommendation, very low-certainty evidence). |
| Implementation considerations |
| From a practical point of view, CPAP is feasible especially with t-piece resuscitator availability in labor and delivery rooms. Despite inclusion of 2 randomized controlled trials, this review shows that the certainty of evidence remains very low. |
| Monitoring and evaluation |
| Rates of NICU admissions and pulmonary air-leak syndromes should be monitored with or without CPAP use in the delivery room among late preterm and term newborns with respiratory distress. |
| Research priorities |
| Large multicenter RCTs are needed to evaluate the effects of early CPAP use in the delivery room for term and late preterm infants with respiratory distress. |

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