QUESTION

Should Sustained inflation vs. Standard PPV be used for newborn infants who receive positive pressure ventilation due to ineffective breathing or bradycardia at birth??

POPULATION:	Newborn infants who receive positive pressure ventilation for ineffective breathing or bradycardia at birth?
INTERVENTION:	Sustained inflation
COMPARISON:	Standard PPV
MAIN OUTCOMES:	Short term mortality (Death during initial hospitalization); Death in the delivery room; Death within first 48 hours; Death at latest follow up; Long term neurodevelopmental or behavioral or education outcomes (> 18 months of corrected age, Test used to assess ND outcome should be of adequate quality and validated); Use of mechanical ventilation during hospitalization; Air leaks (pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema) reported individually or as a composite outcome: at anytime during initial hospitalization ; Air Leaks within first 48 hours; Bronchopulmonary dysplasia, any grade ; Intraventricular hemorrhage: Of any grade ; Intraventricular hemorrhage: grade 3 or above; Retinopathy of prematurity: Of any stage ; Retinopathy of prematurity: stage 3 and above;
SETTING:	Delivery room
PERSPECTIVE:	
BACKGROUND:	The physiologic basis for sustained inflation: Infants at birth have fluid filled lungs. For successful transition, this fluid needs to be replaced with air. { Boon 1979 1031 ,Hooper 2016 266 } Lung aeration is impaired in some infants. These infants present with absent or ineffective breathing at birth, which may be accompanied by bradycardia . { Foglia 2017 360, Lista 2017 360, McCall 2016 175 } Effective ventilation is the key to successful neonatal resuscitation. Current guidelines recommend starting positive pressure ventilation in these infants. { Wyllie 2015 169.} Sustained inflation (SI) breaths at the beginning of positive pressure ventilation may adequately expand the lungs quickly and aid in successful transition. { Bruschettini 2017 4953 .} It can be hypothesized that, by allowing optimal respiratory transition, such maneuvers may improve respiratory outcomes, including improving early cardiorespiratory stability and reducing risk of bronchopulmonary dysplasia. { Foglia 2017 360. Bruschettini 2017 4953, Kirpalani 2019 1165} Evidence for or against sustained inflation: Most newborns are able to clear the fluid in the lungs by generating significant negative pressure (up to -50 cm H2O) during their first few breaths.{ Karlberg 1962 121, Milner 1977 918} However, some infants are unable to clear the fluid and establish optimal lung volume during the first few minutes of life. Preterm infants with weak respiratory muscles and surfactant deficient lungs are more likely to struggle with this transition. { Foglia 2017 360, McCall 2016 175} Boon et al. described that during resuscitation at birth, gas continued to flow and passive inflation occurred in term infants at the end of a 1 second inflation. { Boon 1979 1031 } Based on these observations, when term infants were given an initial inflation of 5 seconds, inflation volume increased 2 fold and facilitated spontaneous respirations.{ Vyas 1981 635} Since then, multiple animal and clinical studies have been conducted. Animal studies have shown SI to be beneficial.{ Crossley 2007 62. Hillman 2013 446. Klingenberg 2013 222. Sobotka 2011 56. Te Pas AB 2016 85. te Pas AB 2009 37. te Pas AB 2009 295} While individual studies have shown reduction in delivery room intubations, improved heart rate and cerebral oxygenation and reduced duration of mechanical ventilation, some observational studies have questioned the effectiveness of SI in infants without spontaneous breaths. { Foglia 2017 360. Lista 2017 360 , McCall 2016 175. Wyllie 2015 169, Fuchs 2011 176. Hunt 2019 17. van Vonderen 2014 903} The recently published SAIL trial, which studied the effect of SI in extreme preterm infants was stopped early due to an increase in 48 hour mortality in sustained inflation arm. {Kirpalani 2019 1165} Potential implications of this systematic review: Guidelines across the world have differing recommendations regarding inflation time and pressure for the first few breaths. For example, ERC guidelines recommend first five breaths that maintain inflation for 2-3 seconds in infants who are gasping or not breathing while ILCOR, AHA and ANZCOR guidelines maintain that there is insufficient evidence to recommend an optimal inflation time. { Wyllie 2015 169, Wyckoff 2015 543. Wyllie 2015 249} SI has become routine practice in some hospitals internationally, but it remains unclear if there is sufficient evidence for this practice. { Foglia 2017 360. McCall 2016 175. Wyckoff 2015 543. Wyllie 2015 249. O'Donnell 2004 583} ILCOR conducted a systematic review and in its 2015 Consensus on Science with Treatment Recommendations (CoSTR), { Wyllie 2015 169} it suggested against routine use of initial SI (greater than 5s duration) for preterm infants but it did allow for consideration of SI in individual clinical circumstances or research settings. (Weak recommendation, low-quality of evidence) The CoSTR statement stressed that there was heterogeneity of methods and absence of long term outcomes in the studies included in the review. The latest Cochrane systemic review (2017)concluded that “SLI followed by nCPAP in the delivery room decreased the need for MV in the first 72 hours of life in preterm infants at high risk of respiratory distress syndrome compared with nCPAP alone but did not decrease the need for respiratory support and the occurrence of BPD”. { Bruschettini 2017 4953.} Amongst various secondary outcomes, only the duration of mechanical ventilation was decreased in SI group. Since this review, further randomized controlled trials including the SAIL trial have been published. {Kirpalani 2019 1165} Given the availability of new studies, it is essential to determine if SI at birth is beneficial or harmful in preterm and term infants. This systemic review has potential to impact ILCOR recommendations regarding SI in newborn infants, the guidelines generated by ILCOR member organizations and worldwide practice.

CONFLICT OF INTERESTS:	The following Task Force members and other authors declared an intellectual conflict of interest and this was acknowledged and managed by the Task Force Chairs and Conflict of Interest committees: The following CoSTR authors were co-authors of cited studies; Aziz K, Liley H, Roehr CC, Schmölzer GM, Trevisanuto D, Urlesberger B

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Clearance of lung liquid (aeration of the lungs) immediately after birth is a crucial step in establishing gas exchange via the lungs. Research in preterm rabbit pups indicates that an initial sustained inflation results in more rapid and stable aeration of the lungs. {te Pas 2009 537} This has led to studies in newborn infants to determine whether a sustained inflation or inflations improves improves outcomes. • te Pas AB, Siew M, Wallace MJ, Kitchen MJ, Fouras A, Lewis RA, Yagi N, Uesugi K, Donath S, Davis PG, Morley CJ, Hooper SB. Establishing functional residual capacity at birth: the effect of sustained inflation and positive end-expiratory pressure in a preterm rabbit model. Pediatr Res. 2009 May;65(5):537-41. • Kirpalani H, Ratcliffe SJ, Keszler M, Davis PG, Foglia EE, Te Pas A, et al. Effect of Sustained Inflations vs Intermittent Positive Pressure Ventilation on Bronchopulmonary Dysplasia or Death Among Extremely Preterm Infants: The SAIL Randomized Clinical Trial. JAMA. 2019;321(12):1165-75 • Abd El-Fattah N, Nasef N, Al-Harrass MF, Khashaba M. Sustained lung inflation at birth for preterm infants at risk of respiratory distress syndrome: The proper pressure and duration. J Neonatal Perinatal Med. 2017;10(4):409-17. • Hunt KA, Ling R, White M, Ali KK, Dassios T, Milner AD, et al. Sustained inflations during delivery suite stabilisation in prematurely-born infants - A randomised trial. Early Hum Dev. 2019;130:17-21. • La Verde A, Franchini S, Lapergola G, Lista G, Barbagallo I, Livolti G, Gazzolo D. Effects of Sustained Inflation or Positive Pressure Ventilation on the Release of Adrenomedullin in Preterm Infants with Respiratory Failure at Birth. Am J Perinatol. 2019;36(S 02):S110-S4. doi: 10.1055/s-0039-1692133. PubMed PMID: 31238370 • Bruschettini M, O'Donnell CP, Davis PG, Morley CJ, Moja L, Zappettini S, et al. Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes. Cochrane Database Syst Rev. 2017;7(7):CD004953-CD	• Guidelines across the world have differing recommendations regarding inflation time and pressure for the first few breaths • Since last ILCOR Systematic review, new large randomized controlled trials have been published. • Given the availability of new studies, it is essential to determine if sustained lung inflation (SLI) at birth is beneficial or harmful in preterm and term infants

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	• For the critical outcome of death within 48 hours, low certainty evidence (downgraded for risk of bias and imprecision) from 10 RCTs {Linder 2005 303; Lista 2015 e457; Schwaberger 2015 e0138964; Mecadante 2016 443; Jiravisitkul 2017 68; Ngan 2017 525; El-Chimi 2017 1273; El-Fattah 2017 409; Kirpalani 2019 1165; La Verde 2019 110} enrolling 1502 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed evidence of harm when initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 2.42; 95% CI 1.15-5.09; I2 = 10%; 18 more patients/1000 died within 48 hours with SI [95% CI, 2 more to 51 more per 1000]) The number needed to harm is 55 [95% CI, 20 - 500]. • When analyzed in subgroup of newborns < 28 + 0 weeks, For the critical outcome of death before discharge, low certainty evidence (downgraded for risk of bias and imprecision) from 5 RCTs {Linder 2005 303; Lista 2015 e457; Jiravisitkul 2017 68; Ngan 2017 525; Kirpalani 2019 1165} enrolling 862 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed evidence of potential harm from initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 1.38; 95% CI 1.00-1.91; I2 = 0%; 46 more patients/1000 died before discharge with the SI [95% CI, 0 fewer to 110 more per 1000]) The number needed to harm is 22[95% CI, 9 - >1000]. • For the all critical and important outcomes except ***Death within 48 hours*** assessed in the metaanalyses of RCTs, the 95% confidence intervals of relative risks (RR) were wide enough to include both potential harm as well as potential benefit. Therefore, it is unclear whether the intervention of interest (sustained inflation) has desirable effects. *See Appendix 1*	•

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	• For the critical outcome of death within 48 hours, low certainty evidence (downgraded for risk of bias and imprecision) from 10 RCTs {Linder 2005 303; Lista 2015 e457; Schwaberger 2015 e0138964; Mecadante 2016 443; Jiravisitkul 2017 68; Ngan 2017 525; El-Chimi 2017 1273; El-Fattah 2017 409; Kirpalani 2019 1165; La Verde 2019 110} enrolling 1502 preterm newborns who received PPV for bradycardia or ineffective respirations at birth showed evidence of harm when initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 2.42; 95% CI 1.15-5.09; I2 = 10%; RD 0.02 (0.00 to 0.03). The number needed to harm is 50 [95% CI, 33 - >1000]. • When analyzed in subgroup of newborns < 28 + 0 weeks, For the critical outcome of death before discharge, low certainty evidence (downgraded for risk of bias and imprecision) from 5 RCTs {Linder 2005 303; Lista 2015 e457; Jiravisitkul 2017 68; Ngan 2017 525; Kirpalani 2019 1165} enrolling 862 preterm newborns who received PPV for bradycardia or	

	ineffective respirations at birth showed evidence of potential harm from initiating PPV with SI >1 s compared to initiating PPV with intermittent inflations lasting ≤1 s per breath (RR = 1.38; 95% CI 1.00-1.91; I2 = 0%; RD 0.05 (0.00 to 0.09). The number needed to harm is 20 [95% CI, 11 - >1000]. • For the all critical and important outcomes except ***Death within 48 hours*** assessed in the metaanalyses of RCTs, the 95% confidence intervals of relative risks (RR) were wide enough to include both potential harm as well as potential benefit. Therefore, it is unclear whether the intervention of interest (sustained inflation) has undesirable effects. *See Appendix 1*	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Please see the same GRADE table in the box for the "desirable effect" in the above.	We considered the overall certainty of evidence as low because, for the all the critical and important outcomes assessed in the metaanalyses of RCTs, there was serious risk of bias and serious imprecision with wide 95% confidence intervals for relative risks (RR).

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	Mortality and neurodevelopmental impairment were deemed critical by the neonatal task force and a larger group of neonatal resuscitation experts who ranked the importance of the outcomes (see abstract). In addition, parents emphasize the importance of these outcomes. Strand M, Simon W, Wyllie J, Wyckoff M, Weiner G. Consensus outcome rating for international neonatal resuscitation guidelines. Arch Dis Child Fetal Neonatal Ed. January 2019.	Although, death within 48 hours is likely to also be an outcomes that parents and clinicians value highly, it may be of lower importance given that for the outcome of death during the entire hospital stay the systematic review could not exclude benefit or harm associated with use of SLI.

	Webbe J, et al. Parent, patient and clinician perceptions of outcomes during and following neonatal care: a systematic review of qualitative research BMJ Paediatrics Open 2018;2:e000343. doi:10.1136/bmjpo-2018-000343	

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	Although for almost all critical and important outcomes, the systematic review could not exclude either benefit or harm resulting from use of SLI. For the outcome of death within 48 hours of life, showed harm associated with the use of SLI. In subgroup of preterm newborns < 28 +0 weeks, the systematic review showed evidence of potential harm .	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	No data available.	Because the outcome of the review did not find a benefit of SI, no additional resources should be required. Had it demonstrated benefit, although there are no published cost data, it is likely that use of SI would require additional resources in resource limited settings. The majority of included RCTs delivered sustained inflation with T-piece resuscitator. Although it can be delivered with flow inflating bag, it cannot be delivered with self-inflating bag. It also requires a compressed gas source.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	No data available	

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 data available	As above, if SI was recommended, it would be likely to result in increased costs in some health care services and hospitals.

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	Because none of these studies have been done in low resourced settings we cannot determine the impact of SLI on health equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No studies have examined acceptability of the intervention, taking into account the results of the systematic review.	Given the increased risk of death within the first 48 hours and absence of proven benefit for other critical and important outcomes, we believe that routine use of SLI for preterm resuscitation will remain unacceptable to many stakeholders. We found no studies comparing sustained inflation </= 5 seconds with standard resuscitation using inspiratory times of < 1 second, but a series of 5short (2-3 second) inflations is recommended routinely in some resuscitation guidelines, implying acceptability in some regions of the world. The acceptability of SLI of other specific durations for SLI remains unknown.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The included studies, conducted in several countries and several of which were multicenter, demonstrates feasibility of the intervention.	Use of sustained inflation is feasible.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendation

For preterm newborn infants who receive positive pressure ventilation due to bradycardia or ineffective respirations at birth, we suggest against the routine use of initial sustained inflation(s) greater than 5 seconds. (weak recommendation, low-quality evidence).

For term or late preterm infants who receive positive pressure ventilation due to bradycardia or ineffective respirations at birth, it is not possible to recommend any specific duration for initial inflations due to the very low confidence in effect estimates.

Justification

This topic was prioritized by the NLS Task Force following completion of a large RCT {Kirpalani 2019 1165} published after the previous CoSTR in 2015.{Perlman 2015 S204}

- In making these recommendations, the NLS Task Force considered the potential for increased death within 48 hours in preterm infants and increased death before discharge in preterm infants <28+0 weeks, a predefined subgroup of the systematic review. The Task Force recognizes that the outcome of death within 48 hours was mainly influenced by one study for which it was one of multiple secondary outcomes. {Kirpalani 2019 1165} The NLS Task Force also considered the absence of evidence for either benefit or harm following sustained inflation at birth for all other critical and important outcomes.

- The comparison of studies was compromised by methodological heterogeneity among studies, including indication, duration, and use of different inspiratory pressure during sustained inflation and the duration for which it was applied.

- No study was identified comparing short duration sustained inflation (< 5 seconds) with intermittent inflations with inspiratory time ≤ 1 second. There is no new evidence to support or refute the practice of inflations < 5 seconds immediately after birth.

- Hunt et al {Hunt 2019 17} was excluded from this systematic review because the control group received short duration sustained inflations (5 inflations of 2-3 s each) and the intervention group, sustained inflations of 15 s duration (ineligible as wrong comparator)

- A patent airway is necessary for effective lung inflation or ventilation. A recent study demonstrated that preterm rabbit pups are prone to closure of the larynx which opens only briefly during a spontaneous breath, and which impedes noninvasive positive pressure ventilation after birth. {Crawshaw 2017 112}. Studies in preterm infants have shown that very little gas enters the lungs in the absence of spontaneous breathing suggesting that the same phenomenon occurs in preterm infants. {Van Vonderen 2014 903, Van Vonderen 2015 514} This PICOST (and most studies) focused on use of sustained inflation on newborns who are not breathing effectively, so inadequate patency of the larynx could explain the absence of benefit from sustained inflation immediately after birth in preterm infants. In addition, the NLS Task Force noted that mask leak or airway obstruction was not measured in the included studies and therefore, whether or not these factors influenced the effectiveness of sustained inflation as applied to the newborns in each study is unknown.

Subgroup considerations

The data for preterm infants suggests possible harm from SI. There were no studies available that examined use of SI in term infants.

No data was available to compare short duration SI (<5 seconds) to intermittent inflations lasting ≤1 s per breath

Implementation considerations

Since no change in current practice is recommended, there are no implications for implementation.

Monitoring and evaluation

No change in current practice is recommended.

Research priorities

- How much of a role does glottis closure play in determining the effectiveness of sustained inflation in newborn infants of different gestations?

- What is the optimal duration, optimal inspiratory pressure and number of sustained inflation maneuvers that allow establishment of functional residual capacity without barotrauma?

- The NLS Task Force recognizes that the total number of infants studied thus far is insufficient to have confidence in the estimate of effect. Larger multi-center trials are needed in both term and preterm newborns to determine whether there are benefits or harms from sustained inflations .

- Studies comparing short duration sustained inflation (< 5 seconds) with intermittent inflations with inspiratory time ≤ 1 seconds are needed. This is an important knowledge gap as the European Resuscitation Council currently recommends maintaining inflation for 2-3 seconds for the first five breaths in infants who are gasping or not breathing.

- Is there a role for sustained inflation for other situations in resuscitation such as cardiac compressions? (For more detail see evidence update for NLS 895 CPR Ratios)

APPENDICES

Appendix 1

Outcomes	With Standard PPV	With Sustained inflation	Difference	Relative effect (95% CI)
Short term mortality (Death during initial hospitalization)	109 per 1,000	**119 per 1,000** (90 to 156)	**10 more per 1,000** (18 fewer to 47 more)	**RR 1.09** (0.83 to 1.43)
Death in the delivery room	2 per 1,000	**6 per 1,000** (1 to 35)	**4 more per 1,000** (1 fewer to 33 more)	**RR 2.82** (0.45 to 17.66)
Death within first 48 hours	13 per 1,000	**30 per 1,000** (14 to 64)	**18 more per 1,000** (2 more to 51 more)	**RR 2.42** (1.15 to 5.09)
Death at latest follow up	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable
Long term neurodevelopmental or behavioral or education outcomes (> 18 months of corrected age, Test used to assess ND outcome should be of adequate quality and validated)	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable
Use of mechanical ventilation during hospitalization	395 per 1,000	**343 per 1,000** (292 to 402)	**51 fewer per 1,000** (103 fewer to 8 more)	**RR 0.87** (0.74 to 1.02)
Air leaks (pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema) reported individually or as a composite outcome: at anytime during initial hospitalization	34 per 1,000	**42 per 1,000** (24 to 74)	**9 more per 1,000** (9 fewer to 41 more)	**RR 1.26** (0.72 to 2.21)
Bronchopulmonary dysplasia, any grade	274 per 1,000	**255 per 1,000** (216 to 301)	**19 fewer per 1,000** (58 fewer to 27 more)	**RR 0.93** (0.79 to 1.10)
Intraventricular hemorrhage: grade 3 or above	94 per 1,000	**82 per 1,000** (59 to 115)	**11 fewer per 1,000** (35 fewer to 22 more)	**RR 0.88** (0.63 to 1.23)
Retinopathy of prematurity: stage 3 and above	128 per 1,000	**106 per 1,000** (79 to 142)	**22 fewer per 1,000** (49 fewer to 14 more)	**RR 0.83** (0.62 to 1.11)