



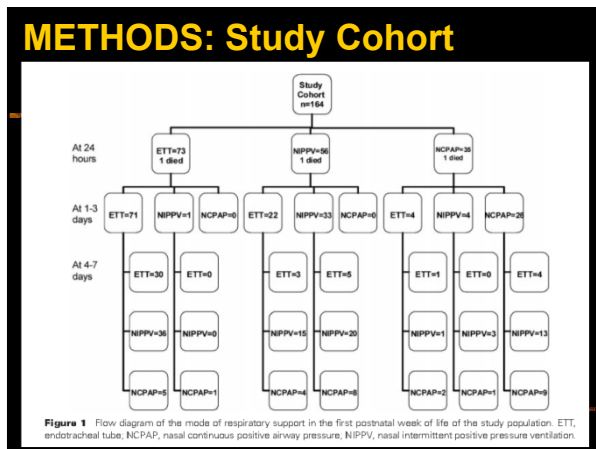
NASAL VENTILATION IN NEONATES

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TYPE and TIMING of VENTILATION in the FIRST POSTNATAL WEEK is ASSOCIATED with BRONCHOPULMONARY DYSPLASIA (BPD)/DEATH

(Dumpa V, et al. Am J Perinatol 2011;28:321-330)



RESULTS: rates of BPD/death

	ETT	NIPPV	NCPAP
@24h	61.6%	62.5%	48.6%
D 1-3	67%	47.4%	55.5%
D 4-7	81.4%	56.8%	40.0%

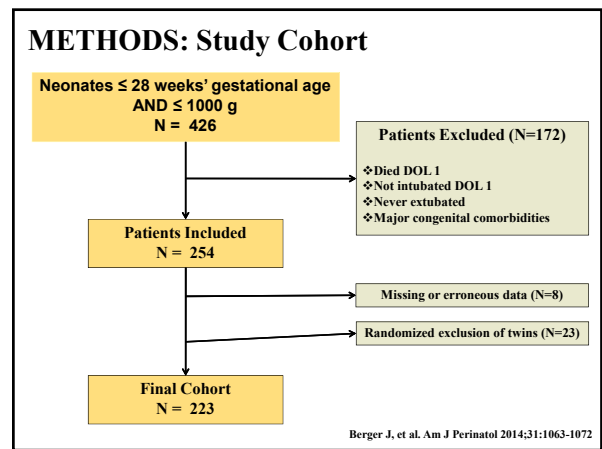
Dumpa V, et al. Am J Perinatol 2011;28:321-330

RESULTS: Primary Outcomes

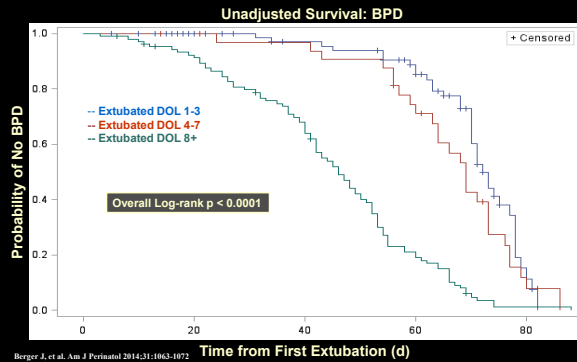
BPD Status	ETT (n = 65)	NIPPV (n = 66)	NCPAP (n = 33)	ETT versus NIPPV, p Value	ETT versus NCPAP, p Value	NIPPV versus NCPAP, p Value
BPD, n (%)	43 (66.2)	29 (43.9)	12 (36.4)	0.037	0.008	0.119
Mild, n (%)	25 (58)	17 (58.6)	12 (100)			
Moderate, n (%)	9 (21)	6 (20.7)	0 (0)			
Severe, n (%)	9 (21)	6 (20.7)	0 (0)			
BPD/death, n (%)	49 (75.4)	38 (57.6)	13 (39.4)	0.031	0.001	0.089

BPD, bronchopulmonary dysplasia; ETT, endotracheal tube; NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation.

Dumpa V, et al. Am J Perinatol 2011;28:321-330



Overall unadjusted survival varies significantly by day of first extubation



Compared to early extubation, late extubation increases risk of BPD

Unadjusted Survival: BPD

Extubation Group	Hazard Ratio	95% Confidence Interval	P-value
DOL 4-7 vs DOL 1-3	1.441	0.877, 2.370	0.1496
DOL 8+ vs DOL 1-3	5.353	3.601, 7.956	< 0.0001
DOL 8+ vs DOL 4-7	3.7137	2.3823, 5.7891	< 0.0001

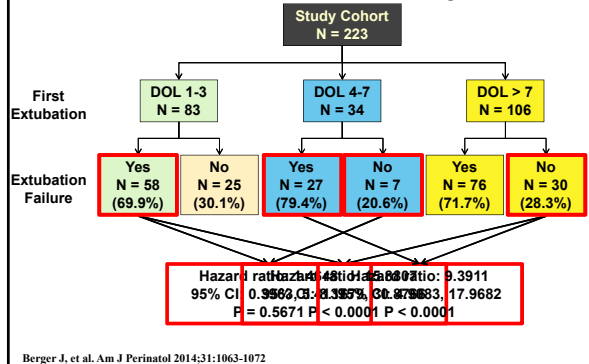
Adjusted Survival: BPD

Extubation Group	Hazard Ratio	95% Confidence Interval	P-value
DOL 4-7 vs DOL 1-3	1.908	1.067, 3.412	0.0292
DOL 8+ vs DOL 1-3	12.671	7.564, 21.228	< 0.0001
DOL 8+ vs DOL 4-7	6.6398	3.9808, 11.0749	< 0.0001

Adjusted for gestational age, race, gender, antenatal steroid use, APGAR scores, multiple gestation, mode of delivery, delivery room resuscitation efforts, surfactant delivery, neonatal comorbidities, and need for reintubation

Berger J, et al. Am J Perinatol 2014;31:1063-1072

Early extubation prevents BPD even when reintubation is necessary



RESULTS: Severity of BPD by extubation DOL

Table 3 Severity of BPD by extubation DOL*

Extubation group	DOL 1-3 (N = 38)	DOL 4-7 (N = 26)	DOL 8+ (N = 107)	p value
Mild BPD, n (%)	21 (55.3)	12 (46.2)	41 (38.3)	0.16
Moderate BPD, n (%)	4 (10.5)	5 (19.2)	14 (13.1)	0.60
Severe BPD, n (%)	13 (34.2)	9 (34.6)	52 (48.6)	0.19

Abbreviations: BPD, bronchopulmonary dysplasia; DOL, day of life.

*Infants with BPD of unknown severity (transferred before 36 weeks' PMA) were excluded from the table.

Berger J, et al. Am J Perinatol 2014;31:1063-1072

TIMING OF EXTUBATION and BPD

- When adjusting for multiple relevant factors, extubation **DOL 1-3** is associated with a **significantly reduced** hazard of BPD when compared to extubation DOL 4-7 or extubation after the first week of life
- Extubation **DOL 4-7** is also associated with a **significantly reduced** hazard of BPD when compared to extubation after the first week of life

Berger J, et al. Am J Perinatol 2014;31:1063-1072

RE-INTUBATION and BPD

- Reintubation rates do not significantly differ across study groups
- Babies who fail early extubation and need to be reintubated are still at a lower risk of BPD than babies who are first extubated later in life and do not need to be reintubated**

Berger J, et al. Am J Perinatol 2014;31:1063-1072

RE-INTUBATION and BPD

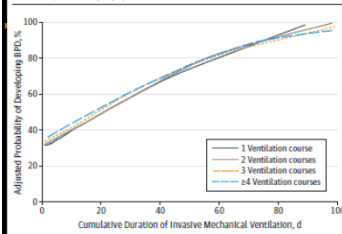
Table 5. Adjusted ORs for Adverse Respiratory Outcomes Among Survivors Obtained From the Logistic Regression Model Inclusive of the Duration of Mechanical Ventilation and the Number of Ventilation Courses

Exposure	Adjusted OR* (95% CI)		
	BPD	Discharged on Oxygen	Tracheostomy
Duration of mechanical ventilation, d			
≤7	1 [Reference]	1 [Reference]	1 [Reference]
8-21	2.44 (1.90-3.13)	1.32 (0.96-1.83)	0.86 (0.04-20.74)
22-35	4.04 (2.90-5.64)	2.14 (1.46-3.13)	2.91 (0.17-48.89)
≥36	7.10 (5.18-9.74)	3.50 (2.30-5.31)	7.80 (0.41-147.23)
No. of ventilation courses			
1	1 [Reference]	1 [Reference]	1 [Reference]
2	1.22 (0.97-1.53)	1.10 (0.83-1.50)	2.13 (0.28-16.04)
3	1.23 (0.92-1.63)	1.03 (0.76-1.41)	0.57 (0.05-6.00)
≥4	1.44 (1.04-2.01)	0.85 (0.56-1.31)	0.96 (0.12-7.67)
Interaction term P value ^b	.15	.14	.07 ^c

Jensen EA, et al. JAMA Pediatr 2015;169:1011-1017

RE-INTUBATION and BPD

Figure. Adjusted Probability of Developing Bronchopulmonary Dysplasia (BPD)



Jensen EA, et al. JAMA Pediatr 2015;169:1011-1017

Our findings suggest that reinitiation of invasive mechanical ventilation does not increase the risk of chronic respiratory morbidity above that attributable to the cumulative duration of mechanical ventilation. A practice of routinely trialing extubation when low ventilator settings are reached, even if extubation success is not guaranteed, may reduce the risk of lung injury and chronic respiratory impairment in extremely preterm infants.

RE-INTUBATION and BPD

- N=224, <27 weeks GA studied
- Infants who were younger at initial extubation spent less time on the ventilator
- 64% infants had to be re-intubated
- Every day first extubation attempt is delayed: \$4555 in extra hospital charges
- Older the infant at first extubation attempt, the more likely the infant will have moderate-to-severe BPD
- Re-intubation not associated with mortality, moderate-severe BPD, or length of stay

Robbins M, et al. J Neonatal-Perinatal Med 2015;8:91-97

A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL COMPARING SYNCHRONIZED NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION (SNIPPV) VERSUS NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (NCPAP)

(Khalaf MN, et al. Pediatrics 2001;108:13-17)

RESULTS

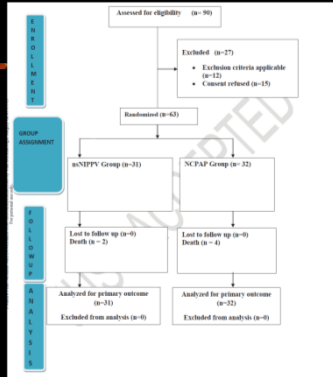
	SNIPPV (n=34)	NCPAP (n=30)	p value
Age at study (d)	4 (1-83)	2.5 (1-106)	0.95
Wt. at study (gm)	1110 ± 55	1200 ± 75	0.32
Pre-MAP (cm H ₂ O)	4.9 ± 0.2	5.1 ± 0.2	0.38
Pre-FiO ₂	0.30 ± 0.02	0.30 ± 0.01	0.84
AR (cm/H ₂ O/L/s)*	169 ± 16	205 ± 21	0.18
LC (ml/cmH ₂ O)*	0.74 ± 0.02	0.8 ± 0.1	0.57
Post-pH	7.36 ± 0.03	7.34 ± 0.02	0.14
Post-CO ₂ (mmHg)	37 ± 1.0	40 ± 2.0	0.06
Apnea (n)	2.24 ± 0.8	2.03 ± 0.7	0.84
Success (n, %)	32 (94)	18 (60)	< 0.01

Data expressed as mean ± sem. *PFTs done on 53/64, 83%

SELECTED SUPPORTIVE STUDIES OF SNIPPV USE IN NEONATES

Author/Year	Type	Mode	N	SNIPPV Group	Control Group	Outcomes
Friedlich 1999	RCT	2 ^a	41	SNIPPV: Rate: 16; PIP: same as pre-extubation; PEEP: 4-6; Ti: 0.8s; FiO ₂ adjusted for SpO ₂ : 92-95%	NP, CPAP: clinician discretion; FiO ₂ adjusted for SpO ₂ : 92-95%	Less failed extubation with SNIPPV
Barrington 2001	RCT	2 ^a	54	SNIPPV: Rate: 12; PIP: 16 (to deliver at least 12); PEEP: 6;	NCPAP: 6	Less failed extubation with SNIPPV
Moretti 2008	RCT	2 ^a	63	SNIPPV: Rate: same as prior to extubation; PIP: 18-20; PEEP: 3-5; Flow: 6-10 L/min; FiO ₂ adjusted for SpO ₂ : 90-94%	NCPAP: 3-5; Flow: 6-10 L/min; FiO ₂ adjusted for SpO ₂ : 90-94%	Less failed extubation with SNIPPV
Bhandari 2009	Retrospective	2 ^a or for apnea	469	SNIPPV: Rate: same as prior to extubation; PIP: increased by 2-4 over pre-extubation values; PEEP: 5; Flow: 8-10 L/min; FiO ₂ adjusted for SpO ₂ : 85-96%	NCPAP: 4-6; Flow: 8-10 L/min; FiO ₂ adjusted for SpO ₂ : 85-96%	SNIPPV group (BW 500-750 g) had decreased BPD, BPD/death, NDI and NDI/death

2^o MODE: NCPAP vs NIPPV



Jasani, B et al. J Matern Fetal Neonatal Med 2016;29:1546-51

2^o MODE: NCPAP vs NIPPV

- The duration of NIV was significantly lower in NIPPV group as compared to NCPAP group (40.4 ± 39.3 hours versus 111.8 ± 116.4 hours, $p = 0.003$)
- The duration of supplementary oxygen was significantly lower in NIPPV versus NCPAP group (84.9 ± 92.1 hours versus 190.1 ± 140.5 hours, $p = 0.002$)
- The rates of BPD in NIPPV group (2/29, 6.9%) were significantly lower than in NCPAP group (9/28, 32.14%) ($p = 0.02$)

Jasani, B et al. J Matern Fetal Neonatal Med 2016;29:1546-51

A RANDOMIZED CONTROLLED TRIAL OF SYNCHRONIZED NASAL INTERMITTENT POSITIVE PRESSURE (SNIPPV) VENTILATION IN RDS

(Bhandari V, et al. J Perinatol 2007;27:697-703)

NICU OUTCOMES

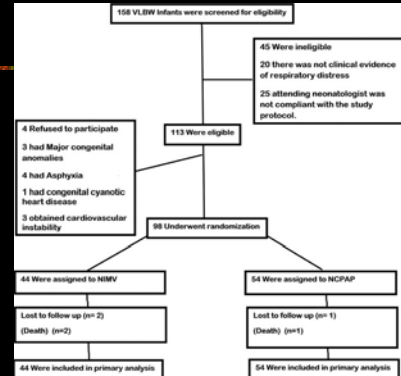
	CV (n=21)	SNIPPV (n=20)	P value
BPD or Deaths (n, %)	11 (52)	4 (20)	0.03
BPD (n, %)	7 (33)	2 (10)	0.04
Deaths (n, %)	4 (19)	2 (10)	0.66
Air leaks (n, %)	1 (5)	1 (5)	1.0
PDA (n, %)	3 (14)	4 (20)	0.70
IVH (n, %)	6 (29)	6 (30)	1.0
PVL (n, %)	1 (5)	2 (10)	0.61
GER (n, %)	5 (25)	2 (10)	0.41
NEC (n, %)	6 (29)	6 (30)	1.0
ROP \geq stage 2 (n, %)	1 (5)	3 (15)	0.34
Total Duration of supplemental O ₂ (days)*	46.8 \pm 6.3	45.5 \pm 6.1	0.88
Total Duration of ETTPPV (days)*	16.6 \pm 3.1	12.7 \pm 2.6	0.17
Total Duration of SNIPPV (days)*	9.8 \pm 2.2	11.7 \pm 2.1	0.27
Length of stay (days)*	65.0 \pm 5.3	61.6 \pm 5.2	0.65

Data expressed as *Mean \pm sem

SELECTED STUDIES OF NIPPV USE IN NEONATES

Author/Year	Type	Mode	N	NIPPV Group	Control Group	Outcomes
Kugelman 2007	RCT	1 ^o	84	NIPPV: Rate: 12-30; PIP: 14-22; PEEP: 6-7; Ti: 0.3s; FIO ₂ adjusted for SpO ₂ : 88-92%	NCPAP: 6-7; FIO ₂ adjusted for SpO ₂ : 88-92%	NIPPV group had decreased BPD
Khorana 2006	RCT	2 ^o	48	NIPPV: Same as pre-extubation ventilator settings	NCPAP: Same as pre-extubation PEEP	No differences in outcomes; however, there were significant differences in the demographics of the 2 groups
Sai Sunil Kishore 2009	RCT	1 ^o	76	NIPPV: Rate: 50; PIP: 15-16; PEEP: 5; Ti: 0.3-0.35s; Flow: 6-7 L/min; FIO ₂ adjusted for SpO ₂ : 88-93%	NCPAP: 5; Flow: 6-7 L/min; FIO ₂ adjusted for SpO ₂ : 88-93%	Less failed extubation with NIPPV

1^o MODE: NCPAP vs NIPPV



Armanian A-M, et al. Int J Prev Med 2014;5:1543-1551

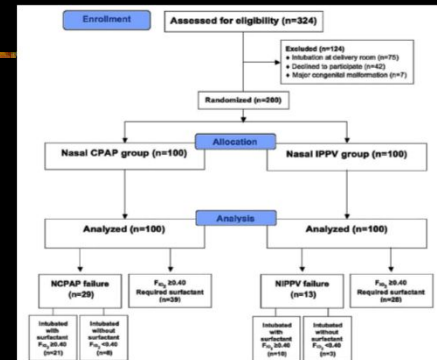
1⁰ MODE: NCPAP vs NIPPV

Outcomes	NIMV (n=44) (%)	CPAP (n=54) (%)	HR (95% CI for HR)	P
Duration of respiratory support (hours) (median (range))	24 (18.00-48.00)	48.00 (22.00-120.00)	-	<0.001 ¹
Need to mechanical ventilation	2 (4.5)	1 (1.9)	0.21 (0.02-2.66)	0.23 ²
Need to HFNC	38 (86.4)	50 (92.6)	0.78 (0.48-1.25)	0.31 ²
Duration of need to HFNC (days) (median (range))	1 (0-3)	2 (0-3)	-	0.009 ³
Duration of oxygen dependency (hours) (median (range))	96.00 (41.00-504.00)	144.00 (70.00-1128.00)	-	0.009 ³
PDA	9 (20.5)	14 (25.9)	0.69 (0.27-1.77)	0.45 ²
IVH	11 (25)	17 (31.5)	0.47 (0.2-1.13)	0.09 ²
Pneumothorax	0 (0)	2 (3.7)	0.96 (0.91-1.2)	0.2 ²
Time to full enteral feeds (days) (mean±SD)	13.72±4.63	16.43±8.26	-	0.045 ²
Duration of hospitalization (days) (mean±SD)	21.59±10.57	28.77±15.85	-	0.009 ³
Deaths	2 (4.5)	1 (1.9)	0.21 (0.02-2.66)	0.23 ²

¹Mann-Whitney test, ²Cox regression (adjusted for age and weight), ³Independent t-test. SD=Standard deviation, NIMV=Nasal intermittent mandatory ventilation, CPAP=Continuous positive airway pressure, HR=Hazard ratio, CI=Confidence interval, HFNC=Humidified high-flow nasal cannula, PDA=Patent ductus arteriosus, IVH=Intraventricular hemorrhage

Armanian A-M, et al. Int J Prev Med 2014;5:1543-1551

1⁰ MODE: NCPAP vs NIPPV with MIST / LISA



Oncel MY, et al. Arch Dis Child Fetal Neonatal Ed 2016;101:F323-8

1⁰ MODE: NCPAP vs NIPPV with MIST / LISA

Characteristics	NCPAP n=100	NIPPV n=100	p Value
Gestational age, mean±SD, weeks	29.1±1.6	29.2±1.7	0.76
Birthweight, mean±SD, g	1175±214	1180±206	0.85
Cesarean delivery, n (%)	73 (73)	68 (68)	0.43
Male, n (%)	48 (48)	49 (49)	0.88
Antenatal steroids, n (%)	85 (85)	86 (86)	0.84
Premature rupture of membrane > 18 h, n (%)	15 (15)	8 (8)	0.12
Apgar score at 1 min, median (min-max)	6 (3-7)	6 (3-8)	0.25
Apgar score at 5 min, median (min-max)	8.5 (8-9)	8.5 (8-10)	0.16
Score for Neonatal Acute Physiology II, mean±SD	28.9±6.5	29.1±6.6	0.83
Multiple pregnancies, n (%)	28 (28)	26 (26)	0.75
Small for gestational age, n (%)	8 (8)	7 (7)	0.78
Maternal pre-eclampsia, n (%)	21 (21)	27 (27)	0.32
Cardiorespiratory status at enrollment			
P _{ao2} , mean±SD (%)	46.6±13.8	49.8±13.9	0.10
S _{po2} , mean±SD (%)	88.6±7.7	87.2±7.3	0.20
P _{ao2} , mean±SD, mm Hg	52.1±10.4	50±9.4	0.13
Respiratory rate, mean±SD, bpm	47.9±12.8	49.7±13.7	0.33
Heart rate, mean±SD, bpm	128±22	130±34	0.56

NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive-pressure ventilation.

Oncel MY, et al. Arch Dis Child Fetal Neonatal Ed 2016;101:F323-8

1⁰ MODE: NCPAP vs NIPPV with MIST / LISA

All subjects	NCPAP n=100	NIPPV n=100	Differences in percentage/average	95% CI of the difference		p Value
				Lower	Upper	
Primary outcomes						
Needed invasive ventilation in the first 72 h of life, n (%)	29 (29)	13 (13)	0.16	0.04	0.27	0.005
Required surfactant, n (%)	69 (69)	38 (38)	0.22	0.08	0.35	0.002
Secondary outcomes						
Duration of NCPAP/NIPPV, median (min-max) days	3 (1-18)	2 (1-29)	0.81	-0.2	1.82	0.12
Duration of invasive ventilation, median (min-max) days	3 (1-29)	2 (1-7)	1.25	-1.37	3.88	0.34
Duration of supplemental oxygen, median (min-max) days	5 (1-38)	3 (1-35)	2.34	0.81	3.86	0.003
Overall rate of intubation, n (%)	37 (37)	20 (20)	0.17	0.04	0.29	0.008
Pneumothorax, n (%)	3 (3)	5 (5)	-0.02	-0.07	0.03	0.47
BPD, n (%) ^a	16 (16)	7 (7)	0.09	0.001	0.18	0.046
Died, n (%)	6 (6)	4 (4)	0.02	-0.04	0.08	0.52
Subjects <30 weeks gestational age	n=62	n=55				
Primary outcomes						
Needed invasive ventilation in the first 72 h of life, n (%)	19 (32)	11 (20)	0.11	-0.04	0.27	0.16
Required surfactant, n (%)	38 (63)	24 (44)	0.19	0.01	0.37	0.034
Secondary outcomes						
Duration of NCPAP/NIPPV, median (min-max) days	4 (1-18)	3 (1-29)	1.02	-0.54	2.59	0.20
Duration of invasive ventilation, median (min-max) days	2 (1-29)	2 (1-7)	1.00	-2.53	4.55	0.56
Duration of supplemental oxygen, median (min-max) days	5 (1-38)	3 (1-35)	2.01	-0.19	4.23	0.064
Overall rate of intubation, n (%)	24 (40)	15 (27)	0.12	-0.04	0.30	0.15
Pneumothorax, n (%)	0 (0)	2 (4)	-0.03	-0.08	0.01	0.14
BPD, n (%) ^a	10 (17)	6 (11)	0.05	-0.07	0.18	0.37
Died, n (%)	5 (8)	3 (6)	0.02	-0.06	0.12	0.54

^aMild-to-severe BPD among survivors to discharge. BPD, bronchopulmonary dysplasia; NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive-pressure ventilation.

Oncel MY, et al. Arch Dis Child Fetal Neonatal Ed 2016;101:F323-8

NCPAP vs NIPPV (± MIST / LISA)

Gestational age (weeks)	No.	Time of assessment of primary outcome	Need to intubation		Need for surfactant		Moderate to severe BPD			
			NCPAP (%)	NIPPV (%)	NCPAP (%)	NIPPV (%)	NCPAP (%)	NIPPV (%)		
Kugelman et al ¹ (2007)	24-34 ^W	84	Within the first 72 h	49	25*	Unclear	Unclear	17	2*	No
Moses et al ² (2011)	26-32 ^W	200	Within the first 72 h	34	25	70	70	5	10.8	No
Ramanathan et al ³ (2012)	26-29 ^W	110	In the first 7 days after surfactant	42	17*	100	100	39	21*	No
Kipalapati et al ⁴ (2013)	<36	1007	Within the first 28 days of life	61.8	59.5	Unclear	Unclear	31	33.9	No
Shi et al ⁵ (2014)	<37	144	At any time	19.2	9.9*	83.5	82.7	Unclear	Unclear	No
Our study (2015)	26-32	200	Within the first 72 h	29	13*	60	38*	16	7*	Yes

*Statistically significant (p<0.05). BPD, bronchopulmonary dysplasia; MIST, minimally invasive surfactant therapy; NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive-pressure ventilation.

Oncel MY, et al. Arch Dis Child Fetal Neonatal Ed 2016;101:F323-8

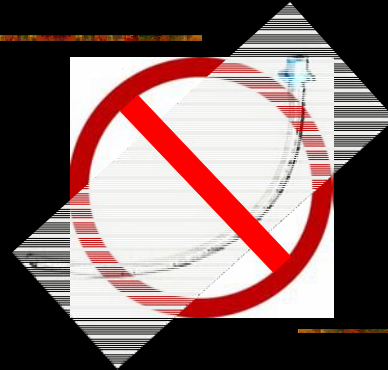
FINAL THOUGHTS

- Attempt to extubate in the first 72h of life
- Efforts should focus on 24h – 72h “window” of opportunity to extubate
- Re-intubation at later postnatal ages does NOT worsen outcomes

FINAL THOUGHTS

- **Secondary mode (S)NIPPV:** Recommended as first choice for extubation
- Recommended to control apnea, escalating from NC to NCPAP to NIPPV, in an attempt to avoid intubation
- Primary mode (S)NIPPV - with or without LISA / MIST: additional RCTs needed for outcome of BPD

LOSE THE TUBE



St. Christopher's Hospital for Children

- **Critical Care Tower**
 - Advanced technology while incorporating families' needs
 - 39 Level IV NICU beds

At St. Chris things have a way of looking UP!

Any questions?