Predictors of Less Invasive Surfactant Administration Failure

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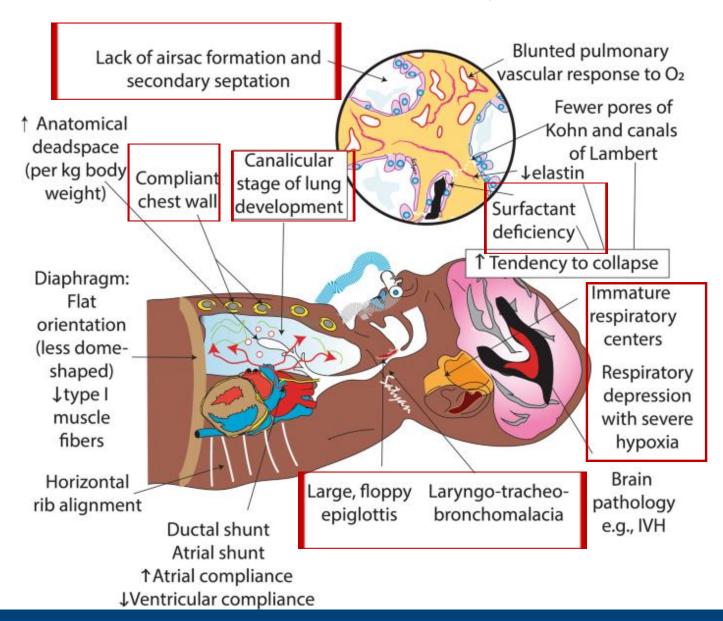




Disclosures

- I have following disclosures:
 - I have received grant support from Chiesi Pharmaceuticals for an ongoing investigator initiated randomized control trial
 - I am a Co-PI of a study on Neonatal Opioid Withdrawal Syndrome conducted by SPARK Biomedical Inc (NIH funded study)
 - | have no actual or potential conflict of interest in relation to this presentation
 - This presentation *will involve* a discussion of an unapproved or off-label use of catheters for less invasive surfactant administration.

Postnatal Transition of Extremely Preterm Infant



Sehgal, Ruoss, Stanford, Lakshminrusimha, & McNamara,

Effects of mechanical ventilation on preterm infants

- Brief exposure to large tidal volume ventilation can induce
 - Widespread lung injury and alveolar protein extravasation making subsequent administration of surfactant less effective ¹
 - Pulmonary and systemic inflammatory response ²
 - Cerebral hemodynamic instability and increased brain inflammation ³

- 1. Bjorklund et al., Ped Res, 1997
- 2. Hillman et al., Am J Respir Crit Care Med, 2007
- 3. Polglase et al., PloS one, 2012
- 4. Hillman et al., Am J Respir Crit Care Med, 2011

Early CPAP Vs Prophylactic MV

	Study design	Results
COIN trial, 2008 GA 25-28 wks (Morley et al., 2008)	CPAP group: Started with CPAP 8 cm H ₂ O Intubation & surfactant criteria: FiO ₂ 0.6, pCO ₂ >60 mm Hg	N=610 ↔ Death or BPD [RR 0.80 (95% CI 0.58-1.12)] CPAP arm: ↓ Need for MV, ↓ MV days, ↑ Air leak
SUPPORT trial, 2010 GA 24-27 wks (Finer & Carlo, 2010)	CPAP group: CPAP 5-7 cm H_2O Intubation & surfactant criteria: $FiO_2 > 0.5 pCO_2 > 65$	N=1316

GA: gestational age, MAP: mean airway pressure, MV: mechanical ventilation, RR: relative risk, PNS: Post natal steroid

Early CPAP vs Prophylactic INSURE*

	Results
CURPAP trial, 2010, GA 25-28 weeks (Sandri et al., 2010)	n= 208 No difference in the need for MV w/in 5 days (RR 0.95 (95% CI 0.64-1.41) INSURE group: 10% infants could not be extubated after INSURE 30% required reintubation within 5 days after INSURE in DR CPAP group: 50% infants required no intubation/MV (within 5 days)
DRM trial, 2011 GA 26-29 weeks (Dunn et al., 2011)	n=439 No difference in death/BPD (RR 0.83 (95% CI 0.64-1.09) INSURE group: 41% required reintubation within first week CPAP group 48% required no intubation/MV within first week

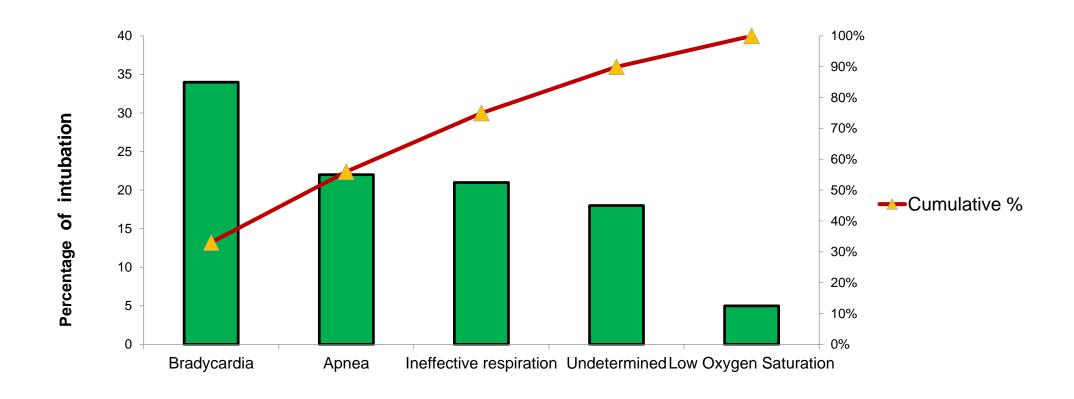
^{*}INSURE: Intubate-Surf-Extubate

Early CPAP Compared to Mechanical Ventilation: Early CPAP Improves Outcome

Author	Result	RR/NNB (95% Conf Int)
Subramanian et al; Cochrane Database of Systematic Reviews 2016 RCTS: 3	↓ BPD in DR-CPAP group	RR 0.89, (0.8 to 0.99) NNB 25 (13-100)
N= 2364	↓ Death or BPD in CPAP group	RR 0.89, (0.81-0.97) NNB 20 (11-100)
	← Mortality	RR 0.82, (0.66 to 1.03)

RR: relative risk, NNB: number needed for treatment benefit

Evaluation of reasons for intubation

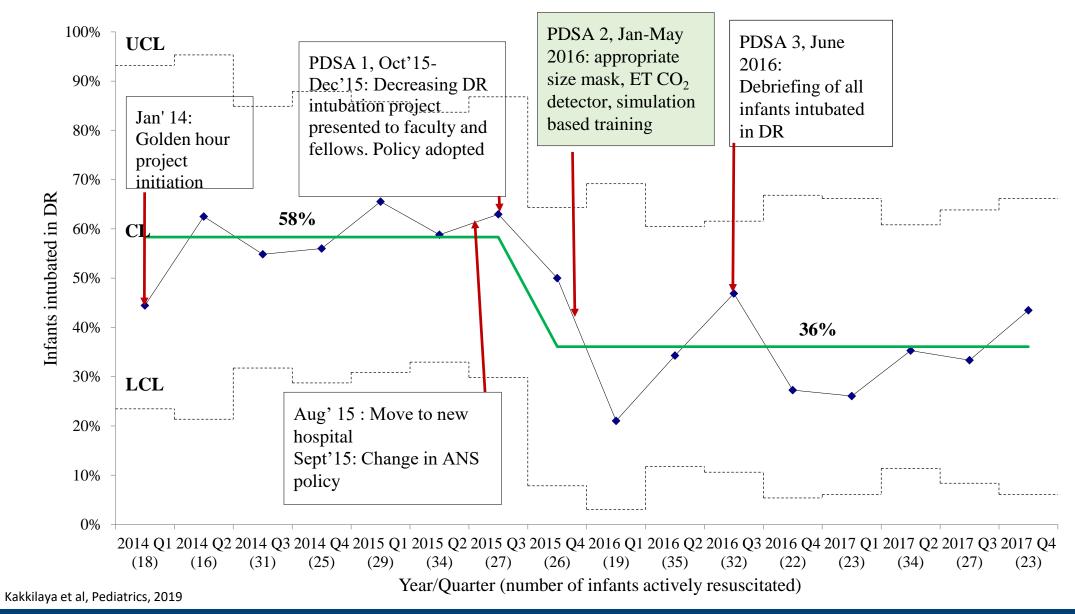


Reasons for intubation

Interventions to Decrease Delivery Room Intubation

- ✓ Reemphasize importance of ventilation corrective measures; MRSOPA, especially increase PIP to 30 and I Time to 1s
- ✓ Use of round mask and appropriate size
- ✓ RT training in decreasing mask leak + obstruction using simulation
- ✓ Use ETCO₂ during bagging to assist adequate ventilation
- ✓ Debriefing after every intubation in the NICU
- ✓ Document reason for intubation

Decreasing Delivery room intubation rate with resuscitation bundle to improve face mask positive p



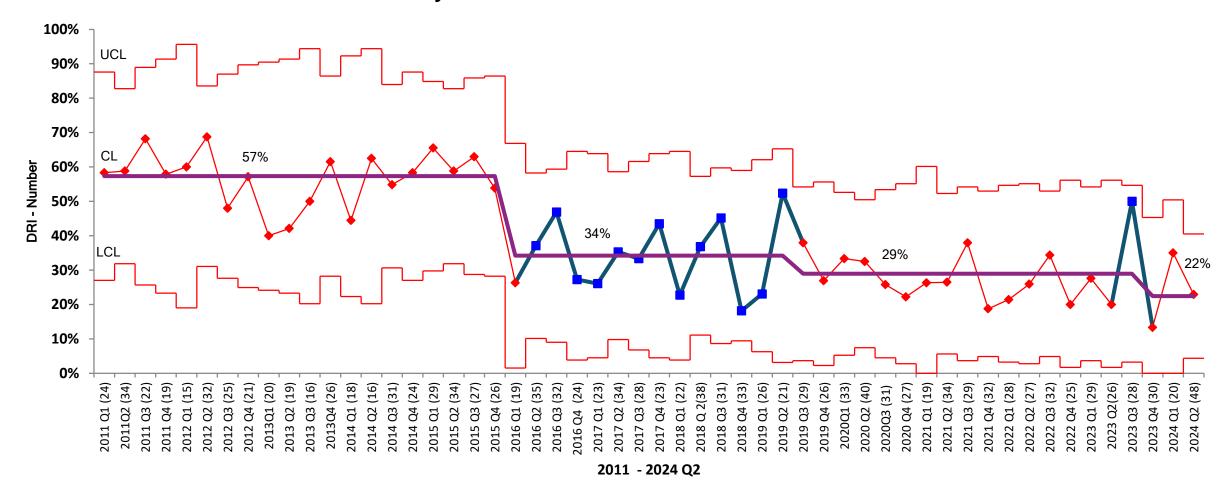
Decreasing DR Intubation Rates Improve Outcomes

	Pre QI N=180	Post-QI N=134	P-value
BPD (%)*	47 (26)	17 (13)	<0.01
Severe ROP (%)	25 (14)	7 (5)	0.01
Severe IVH (%)	21 (12)	10 (8)	NS
Death (%)	19 (11)	16 (12)	NS
Death or BPD (%)	66 (37)	33 (25)	0.02

Kakkilaya V et al, Pediatrics, 2019

^{*}Walsh et al, 2006

Delivery Room Intubation Rate 22-29 weeks GA



CPAP Failure*

Need for Mechanical ventilation within 72 hours in the CPAP arm of randomized control trials

	GA (weeks)	Criteria for surfactant therapy	CPAP failure**
Morley et al., 2008	25-28	FiO ₂ >0.6, CPAP 8	46 %
Finer et al., 2010	24-27	FiO ₂ >0.5, CPAP 5-7	52%
Sandri et al., 2010	25-28	FiO ₂ >0.4, CPAP 5-7	48%
Dunn et al, 2011	26-29	FiO ₂ 0.4-0.6, CPAP 5-7	46%

^{*}Need for mechanical ventilation within 72 hours of life

Predicting CPAP Failure in ≤ 29 weeks GA infants

	FiO ₂ threshold
Fuchs et al, 2011	$FiO_2 \ge 0.3$ on admission
Dargaville et al, 2013	FiO ₂ ≥ 0.3 within 2 hours of life
Kakkilaya et al, 2019	FiO ₂ > 0.3 at 2 hours of life
Gulczynska et al, 2019	FiO ₂ ≥ 0.29 at 2 hours of life

CPAP failure is associated with higher odds of

- Pneumothorax
- BPD
- Severe IVH
- Mortality

^{*}Need for mechanical ventilation within 72 hours of life

Optimizing CPAP therapy

- Bubble CPAP improves oxygenation¹
- Appropriate size nasal prongs ↓ resistance to flow and pressure drop ²
- Proper positioning of the infant ³
- Higher CPAP level increase functional residual capacity 4, 5, 6
- Mouth closure improves CPAP transmission ⁷
- Avoid gastric distension with venting ⁶
- Frequent monitoring/checks ⁸

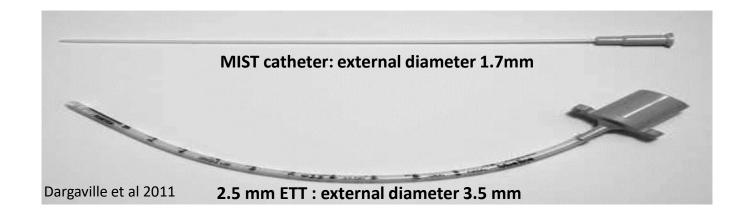
- 1. Courtney SE et al, 2011
- 2. Green EA et al, 2019
- 3. Wright, CJ et al, 2018
- 4,5,6: Gregory GA, 1969, Bonta et al 1977, Bhatia et al 2017
- 7. De Paoli et al, 2005
- 8. Sahni & Wung 1998

Higher Resistance Nasal Interface = Greater Drop in Delivered Pressure

Interface	Outer Diameter (mm)	Expiratory Limb Pressure (cm H ₂ O) @ 8L/min flow
Hudson 0 3	3.6 5.1	7.8 (= 0.94
F&P prong Small Medium	2.8 3.9	12.2 (-1.9
F&P Mask small	4	0 🛑
RAM Premie Newborn	3.1 4.5	10.9 (9.4

Surfactant Administration Without Invasive Positive Pressure Ventilation

- Aerosolized surfactant
- Surfactant Through Laryngeal or Supraglottic Airway (SALSA)
- Thin catheters using direct laryngoscope or video-laryngoscope
 - Cologne method: 4 Fr feeding tube with using Magill forceps ¹
 - Minimally Invasive Surfactant Therapy technique using 16 G, 5.5" vascular catheter ²



- 1. Kribs et al, 2007
- 2. Dargaville et al 2011

Clinical Trials

20 trials compared LISA vs surfactant administration using ETT

Strategies in the control group	# RCT(s)
Intubation, surfactant administration followed by continued MV	1
Selective intubation and continued MV. Surfactant per the discretion of clinician	4
INSURE using similar threshold as LISA group	15

LISA: Less Invasive Surfactant Administration,

MV: mechanical ventilation, ETT: endotracheal tube,

RCT: randomized control trials

Kakkilaya V, Gautham KS, Ped Res. 2022

LISA vs Intubation, Surfactant and Continued MV

Author/Year/ Design	LISA Group	Control group	Results
Kribs et al, JAMA Pediatr, 2015, 13 centers 23 -26 weeks GA Enrolled ≤ 2 hours of life Poractant alfa, 100 mg/kg	Threshold for surf: $FiO_2 > 0.3$, Silverman score ≥ 5 Procedure: Cologne method, Premedication: None Intubation criteria: $FiO_2 \geq 0.45$, $PaCO_2 > 60$, persistent apnea.	Threshold for surf: FiO ₂ >0.3 Silverman score ≥5 Continued MV after surfactant	n=211 → Survival without BPD * ↑ Survival without major complications ↓ Need for MV ↓ Pneumothorax ↓ Grade 3-4 IVH

^{*}Primary outcome; aRR: absolute risk reduction

LISA vs CPAP, Selective intubation ± Surfactant via ETT

Author/Year/ Design	LISA Threshold	Control Group	Result
Dargaville et al, JAMA, 2021	$FiO_2 \ge 0.3$,	Sham Treatment	n=485 (of the desired 606)
33 centers, 25-28 weeks GA	CPAP 5-8 cm H ₂ O	CPAP 5-8 cm H2O	
Enrolled within 6 HOL	MIST method		→ Death or BPD (43.6 % v s 49.6)* RR 0.87 (95% CI 0.74 to 1.03)
Treatment team blinded to	Intubation criteria:	Intubation criteria:	, , , , , , , , , , , , , , , , , , ,
group allocation	FiO ₂ ≥0.45,	FiO ₂ ≥0.45,	↓ BPD, pneumothorax, need for MV
Study period:	persistent apnea	persistent apnea.	≤ 72 hours, PDA treatment,
Dec 2011- March 2020	If intubated,	If intubated,	
Enrollment stopped due to slow recruitment	surfactant per clinician's discretion	surfactant per clinician's discretion	RR 1.27 (95% CI 0.63 to 2.57)
Surf: Poractant alfa 200 mg/kg			

^{*} Primary outcome

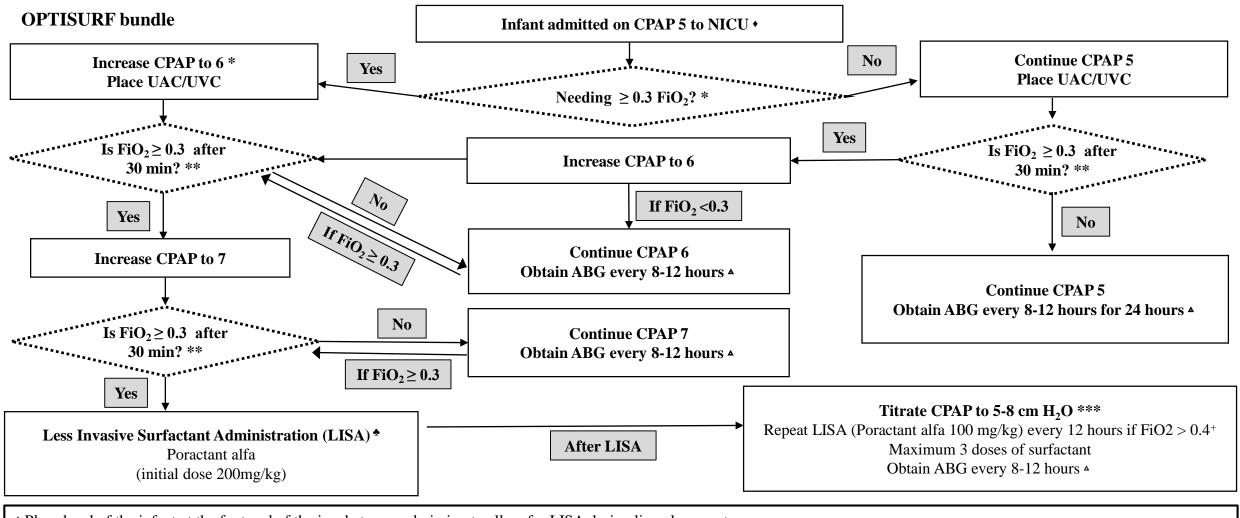
LISA vs CPAP Selective Surfactant via ETT*

Author/Year/ Design	LISA Group	Control Group	Result
Katheria, A NEJM evidence, 2023 24-29 weeks GA Multicenter study Enrolled within one hour. 2 centers in US	Caffeine + LISA given within 2 hours of life	Surfactant via ETT for CPAP 6-8cm H ₂ O, FiO ₂	N= 180 LISA group: ↓ Need for MV within 72 HOL (23% vs 53%) ↓ BPD (26 % vs 39%)

^{*}INSURE or Continued MV

Meta-analysis

Author, # RCTs, n	Results, Risk Ratio (95% CI), NNB (95% CI)
Abdel-Latif et al, 2021	LISA vs ETT surfactant (all studies)
16 RCTs	LISA associated with:
	↓ BPD 0.57 (0.45, 0.74) NNB 13 (9-24)
	↓ MV within 72 hours, 0.63 (0.54 to 0.74) NNB 8 (6-12)
	↓ Severe IVH, 0.63 (95% CI 0.42 to 0.96), NNB 22 (12-193)
	↓ Mortality 0.63 (95% CI 0.47,0.84), NNB 20 (12-58)
	LISA vs INSURE
	↓ Death or BPD, RR 0.66 (95% CI 0.46 to 0.93), NNB 11 (6-15) ←
	↓ MV within 72 hours, (RR 0.52, 95% CI 0.4, 0.68), NNB 9 (6-12)



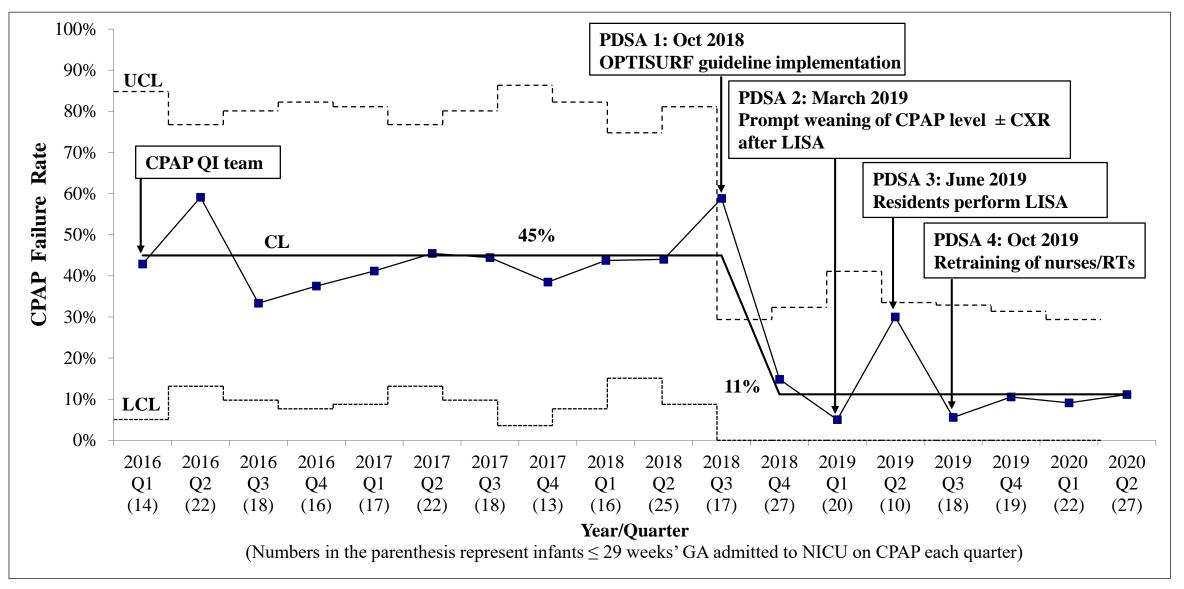
- ♦ Place head of the infant at the foot end of the incubator on admission to allow for LISA during line placement
- ▲ If no UAC, obtain CBG
- * Intubate if requiring $FiO_2 \ge 0.7$ or having frequent apnea (≥ 3 in one hour needing stimulation or any needing PPV)
- ** If requiring $FiO_2 \ge 0.5$, intervene at 20-minute intervals
- *** Wean CPAP to 6 if $FiO_2 < 0.25$ after surfactant and obtain CXR within 2 hours s/p LISA and wean for hyper-expansion Avoid rapid wean of pressure in <26 weeks' GA infants and those without antenatal steroids
- + Intubate if needing FiO₂ > 0.45 on CPAP \geq 7 cm H₂O for > 1 hour after LISA, or if not due for next dose
- ♣ Keep head midline. Do not change infant's position while administering LISA.\

Catheter insertion depth:

≤ 26 week : 1cm 27-28 week: 1.5 cm >28 week: 2 cm

Kakkilaya et al, Pediatrics, 2021

CPAP Failure Rate



Kakkilaya et al, Pediatrics, 2021

CL: Control line, UCL: Upper control limit, LCL: Lower control limit, PDSA: Plan do study act, CXR: Chest radiograph

Comparison of respiratory care of infants in pre vs post QI

	All infants		23-26 weeks' GA		27-29 weeks' GA	
Characteristics	Pre QI	Post-QI	Pre-QI	Post-QI	Pre-QI	Post-QI
	n=125	n=91	n=33	n=28	n=92	n=63
CPAP failure n (%)	68 (54)	10 (11)*	26 (79)	8 (27)*	42 (46)	2 (3)*
MV within 7 days	70 (56)	12 (13)*	27 (82)	10 (36)*	43 (47)	2 (3)*
Any MV n (%)	72 (58)	28 (31)*	25 (76)	16 (57)	47 (51)	12 (19)*
HFV n (%)	30 (24)	5 (6)*	21 (64)	4 (14)*	9 (10)	1 (2) •
MV days δ	4 (1, 11)	2 (0, 12)	10 (3, 25)	5 (2, 27)	1 (1, 7)	1 (0, 2)*
NIPPV n (%)	15 (12)	15 (17)	8 (24)	12 (43)▲	7 (8)	3 (5)

δ Median (25th, 75th), * P=<0.01, ** P= <0.05, **♣** P=0.053, **▲** P=0.06

Comparing Outcomes Between Pre and Post-QI Cohorts

	All in	fants	23-26 w	eeks GA	27-29 w	reeks GA
Characteristics	Pre OSC n=125	Post-OSC n=91	Pre-OSC n=33	Post-OSC n=28	Pre-OSC n=92	Post-OSC n=63
Pneumothorax n (%)	10 (8)	1 (1)**	5 (15%)	0*	5 (5)	1 (2)
Pulm Hemorrhage n (%)	4 (3)	4 (4)	2 (6)	4 (14)	2 (2)	0 (0)
PDA treatment n (%)	26 (21)	8 (9)**	15 (46)	6 (22)**	11 (12)	2 (3)*
NEC n (%)	10 (8)	7 (8)	5 (15)	0	5 (5)	7 (11)
Severe IVH n (%)	5 (4)	4 (4)	2 (6)	4 (14)	3 (3)	0
Severe ROP n (%)	8 (6)	3 (3)	5 (15)	3 (11)	3 (3)	0
BPD n (%)	20 (16)	8 (9)	12 (36)	7 (25)	8 (9)	1 (2) •
Home oxygen n (%)	4 (3)	4 (5)	3 (9)	4 (14)	1 (1)	0
Mortality n (%)	9 (7)	8 (9)	6 (18)	7 (25)	3 (3)	1 (2)
Death or BPD n (%)	29 (23)	16 (17)	18 (55)	14 (50)	11 (12)	2 (3) *
Length of stay δ	80 (62, 105)	72 (59, 96)	105 (87, 136)	96 (60, 123)	72 (59, 90)	70 (59, 85)

Can We Predict LISA Failure?

LISA Failure: Need for MV within 72 hours after LISA

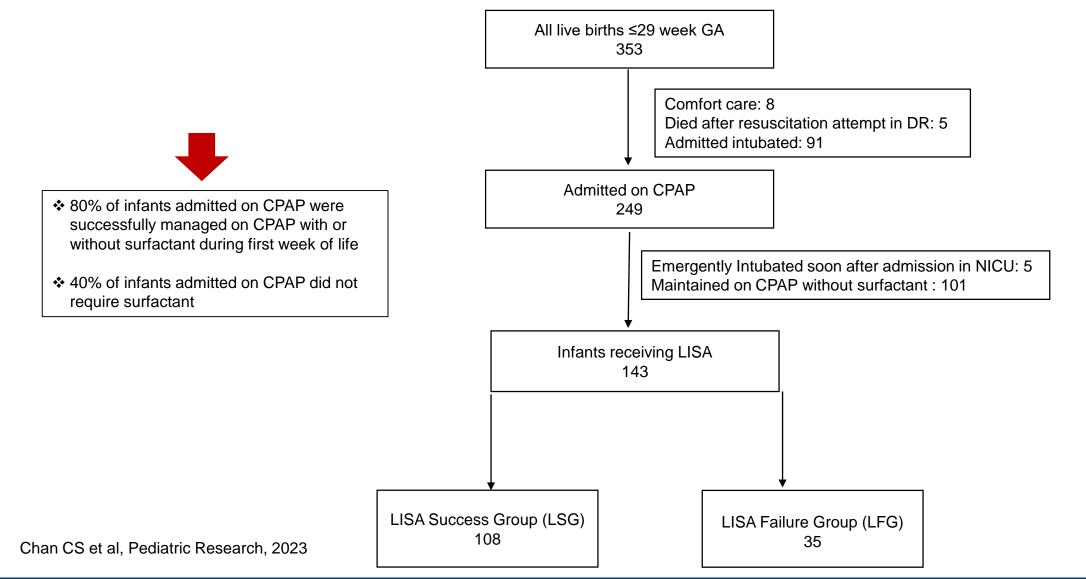
LISA Failure* in RCTs

Author, year	GA	Threshold for LISA	LISA failure
Kanmaz et al. 2012	23-32 weeks GA	FiO ₂ >40 %, CPAP 5-7 cm H ₂ O	30 %
Kribs et al. 2015	23-26 weeks	FiO ₂ >30 % and/or Silverman score ≥5	47 %
Dargaville et al. 2021	25-28 weeks	$FiO_2 > 30 \%$, CPAP 5-8 cm H_2O	36 %
Katheria et al. 2023	24-29 weeks GA	Infants needing CPAP	23%

LISA Failure in Infants ≤ 26 week GA

- Retrospective cohort study of infants 22-26 week GA born in 68 NICUs in German Neonatal network between 2009-2020. LISA was administered in DR
- Results: Of the 6542 enrolled infants, 7% did not receive surf, 38% received LISA, 54% received ETT surf.
- LISA Failure: 46%
- Compared to ETT surf group, LISA was independently associated with decreased mortality and death or BPD.
 No difference in sIVH
- LISA Failure was associated with GA, male gender, no ANS, out born status, low Apgar score, IUGR status, and higher max FiO₂ (>0.6) in the first 12 HOL

Flow chart of ≤ 29 week GA infants born 2018 Q4-2021



Comparison of LISA Success and LISA failure Groups

	LISA Success (n = 108)	LISA Failure (<i>n</i> = 35)	<i>P</i> -value
Mother's Age, yr*	28 (24, 35)	26 (21, 30)	0.03
Hispanic, n (%)	69 (64)	23 (66)	0.90
Antenatal Steroids, n (%)	93 (86)	28 (80)	0.55
Complete Course (=2), n (%)	41/93 (44)	14/28 (48)	0.58
Prolonged ROM (>18 hours), n (%)	30 (28)	10 (29)	0.93
Multiple birth, n (%)	19 (18)	8 (23)	0.49
Cesarean section, n (%)	79 (73)	29 (83)	0.25

^{*}Median (25th, 75th)

Comparison of LISA Success and LISA failure Groups

	LISA Success n = 108	LISA Failure n = 35	<i>P</i> -value
Male, <i>n</i> (%)	54 (50)	19 (54)	0.66
Estimated GA, weeks*	27 (26, 29)	25 (24, 27)	<0.01
Estimated GA ≤ 25 weeks, <i>n</i> (%)	22 (20)	18 (51)	<0.01
Apgar scores			
1 min*	4 (3, 6)	3 (2, 4)	0.02
5 min*	7 (6, 8)	7 (6, 8)	0.08
Cord Blood gas pH*	7.27 (7.22, 7.31)	7.29 (7.26, 7.34)	0.11
Cord Blood gas base deficit*	-5.3 (-8.6, -3.7)	-4.7 (-6.9, -2.5)	0.14
Hypothermia (<36° C) on admission, n (%)	18 (17)	5 (14)	0.74
Hypothermia ($< 36^{\circ}$ C) ≤ 4 hrs of life, n (%)	31 (29)	20 (57)	<0.01

^{*}Median (25th, 75th)

Comparison of DR and NICU Respiratory Support

	LISA Success n = 108	LISA Failure n = 35	<i>P</i> -value
Max FiO ₂ in DR*	0.75 (0.60, 1)	1 (0.7, 1)	<0.01
Max CPAP, cm H ₂ O*	5 (5, 6)	6 (6, 7)	<0.01
FiO ₂ *	0.30 (0.23, 0.37)	0.40 (0.25, 0.5)	<0.01
CPAP*	5 (5, 6)	6 (6, 7)	<0.01
FiO ₂ @ 1 hour of life *	0.30 (0.25, 0.38)	0.40 (0.25, 0.58)	0.04
CPAP @ 1 hour of life *	6 (5, 6)	7 (6, 7)	<0.01
Time of birth to LISA (hrs)*	3.93 (2.45, 11.23)	2.00 (1.20, 3.77)	<0.01
FiO ₂ 1 hour after LISA*	24 (21, 28)	30 (24, 45)	<0.01
CPAP 1 hour after LISA *	6 (6, 7)	7 (6, 7)	<0.01
>1 dose of LISA, <i>n</i> (%)	17 (16)	14 (40)	<0.01

^{*}Median (25th, 75th)

Chan CS et al, Pediatric Research, 2023

Comparison of DR and NICU Respiratory Support

	LISA Success (n=108)	LISA Failure (n=35)	<i>P</i> -value
MV during first week of life, n (%)	4 (4)	35 (100)	<0.01
MV during hospital stay n (%)	23 (21)	35 (100)	<0.01
HFV (HFOV/HFJV), n (%)	6 (6)	15 (43)	<0.01
Pneumothorax, n (%)	2 (2)	3 (9)	0.09
Pulmonary hemorrhage, n (%)	2 (2)	10 (29)	<0.01
BPD, n (%)	16 (15)	9 (26)	0.14
NEC, n (%)	7 (7)	3 (9)	0.71
Severe ROP (=3 either eye), n (%)	9 (8)	8 (23)	0.03
Severe IVH (>3 right or left), n (%)	2 (2)	7 (20)	<0.01
Death or Moderate to severe BPD, n (%)	19 (18)	20 (57)	<0.01

LISA Failure by Gestational Age

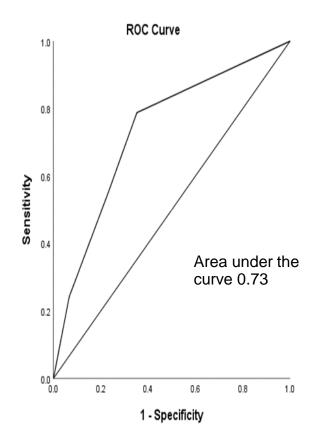
GA	All infants n=244	CPAP success n=209	CPAP failure n=35	CPAP Success %
22-23	2	0	2	0
24	18	11	7	61
25	23	14	9	61
26	25	19	6	76
27	54	48	6	88
28	53	50	3	94
29	69	67	2	97

Reasons for LISA Failure

	Reasons for LISA Failure (n=35)
Apnea, <i>n</i> (%)	15 (43)
Hypoxemia, n (%)	12 (34)
Pneumothorax, n (%)	3 (9)
Hypercarbia, n (%)	1 (3)
IVH, n (%)	1 (3)
Pulmonary hemorrhage, n (%)	2 (6)
Hemodynamic instability, <i>n</i> (%)	1 (3)

Predictors of LISA failure

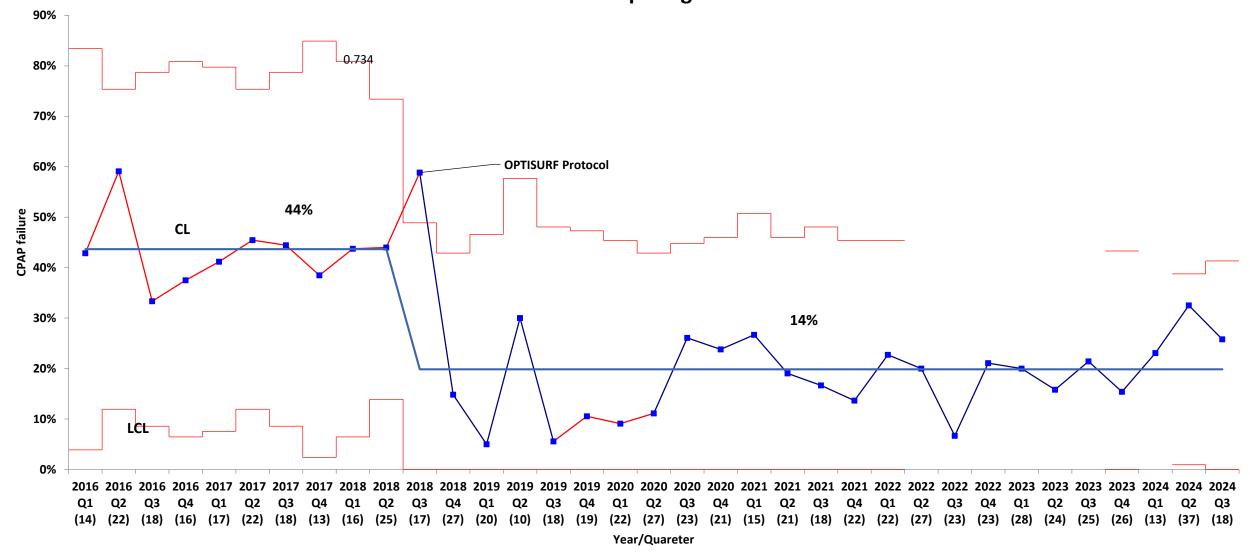
- GA ≤ 25 weeks (aOR 3.62, (95% CI) 1.51-8.68, P <0.004
- FiO₂ ≥0.30 an hour after LISA (aOR 3.69, CI 1.57-8.67, P 0.003)



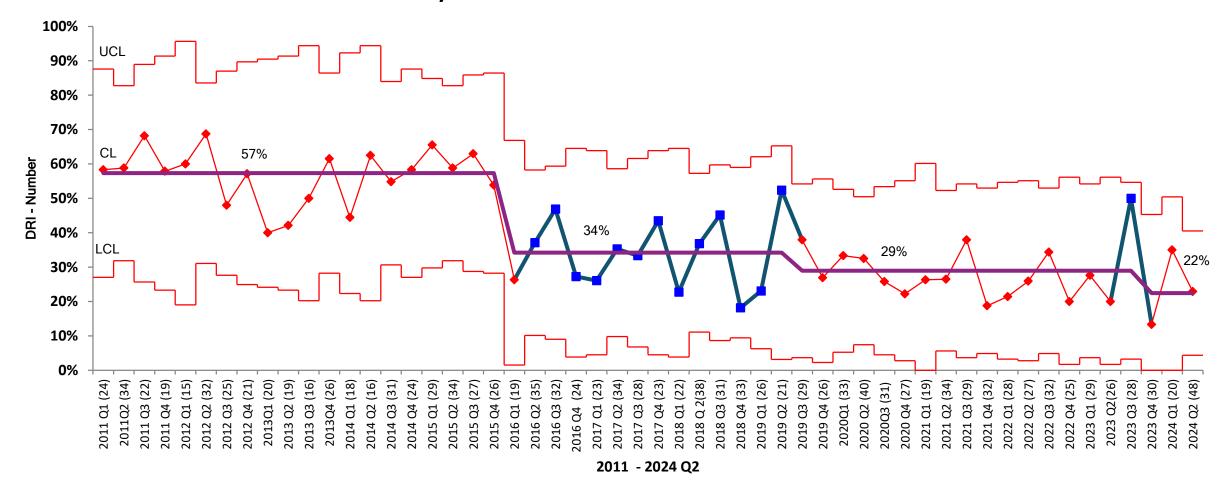
How to decrease the need for MV in ≤ 25 weeks GA infants?

- Delayed cord clamping
- Prevent hypothermia
- Support spontaneous breathing: Early caffeine
- Maintain adequate FRC:
 - Higher CPAP level when needed
 - Non Invasive Positive Pressure Ventilation: sNIPPV, NAVA, nHFOV
 - Repeat doses of surfactant

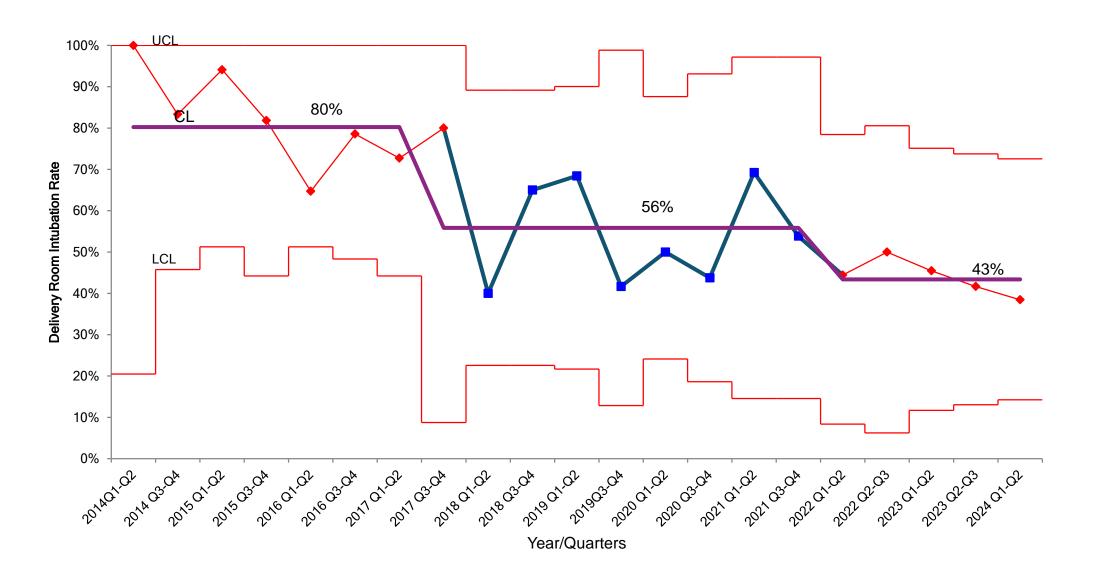
% of infants admitted on CPAP requiring MV within 72 hours

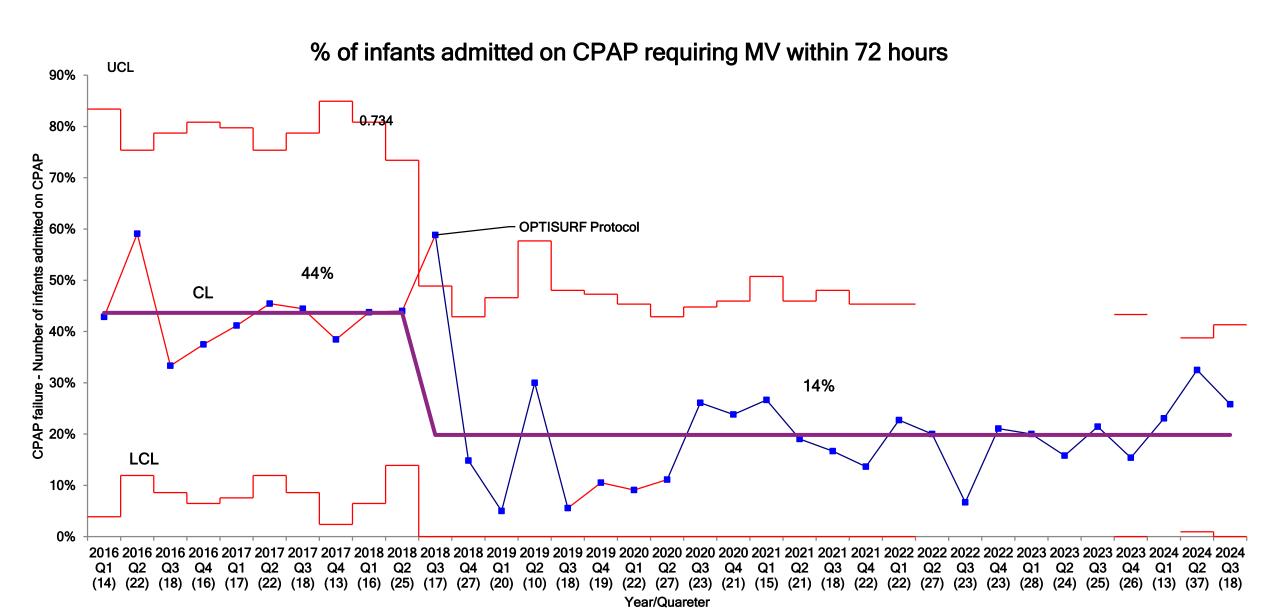


Delivery Room Intubation Rate 22-29 weeks GA

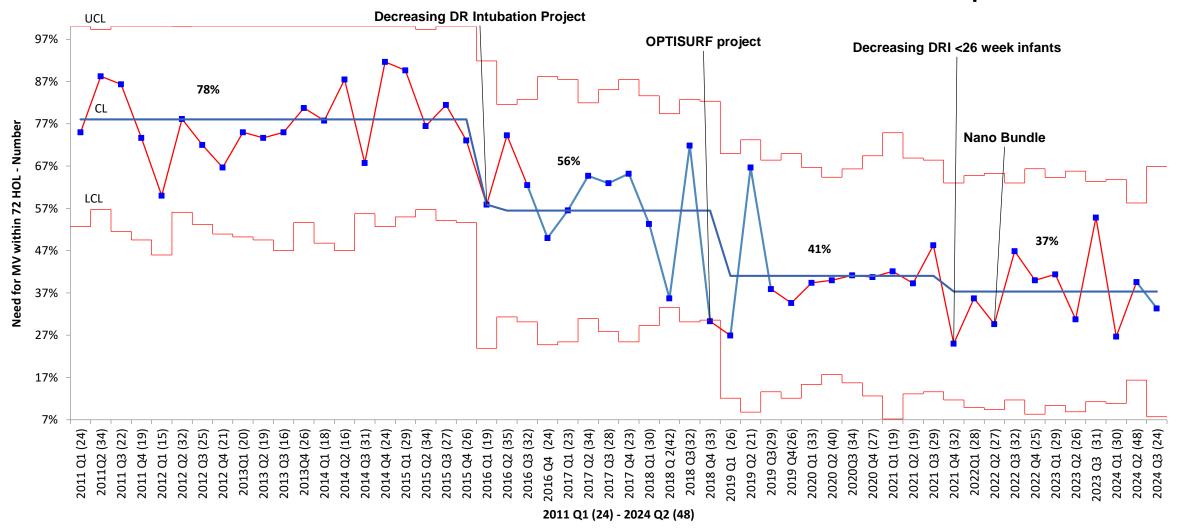


Delivery Room Intubation Rate in 22-25 weeks gestational age infants





Need for MV within 72 HOL for all infants ≤29 weeks GA p Chart

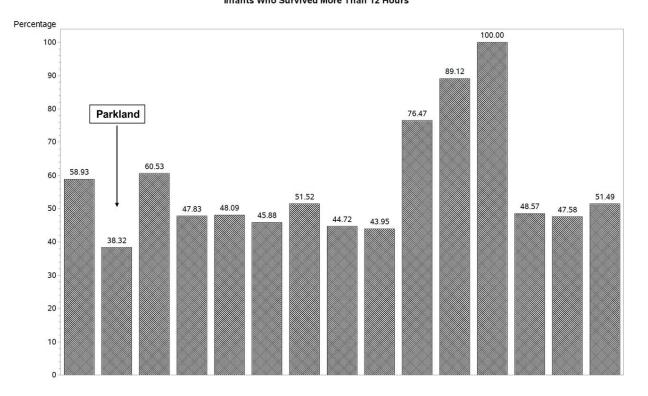


Bronchopulmonary Dysplasia (BPD)

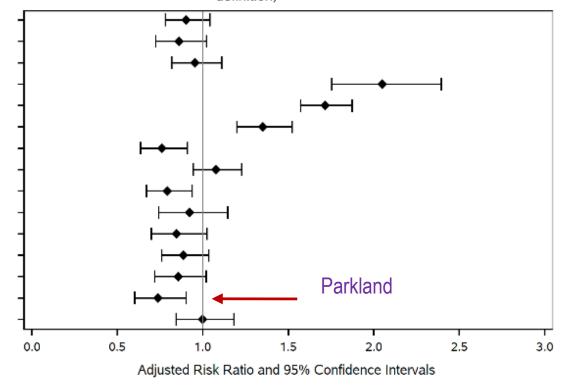
Comparison of Parkland NICU vs. NICHD Neonatal Research Network (NRN) Centers

Center

GDB Infants Born Between January 2022 and December 2022
Inborn and Birth Weight 401-1000 grams or Gestational Age < 29 Weeks
BPD (traditional)
Infants Who Survived More Than 12 Hours

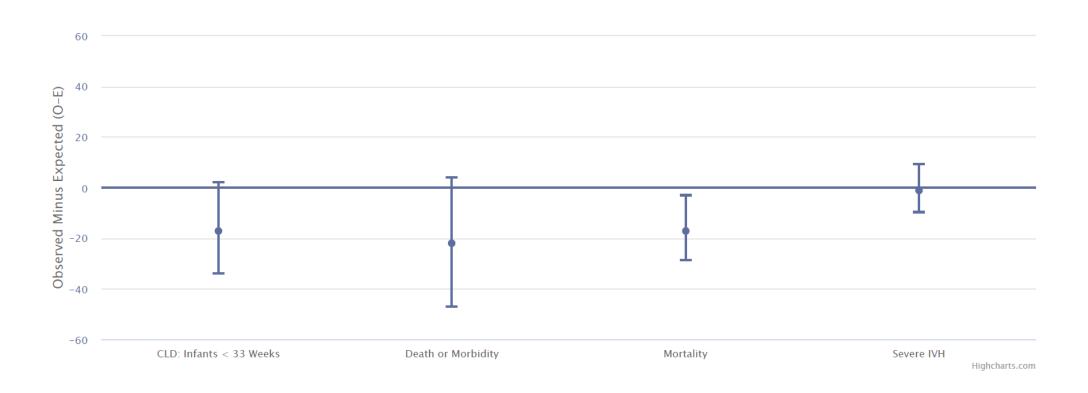


Center-specific Adjusted Risk Ratio and 95% Confidence Interval for BPD (Traditional definition)



*GDB = NICHD Neonatal Research Network Generic Database of 15 large academic centers in the USA

How do we compare with VON centers?



Summary

- Avoiding MV and stabilization of preterm infants on CPAP at birth improves outcomes.
- Large body of evidence supports LISA using thin catheter in preterm infants
- Our single center experience shows that implementation of QI bundle consisting of stepwise escalation of CPAP and LISA guided by FiO₂ ≥ 0.3 decrease the need for MV, PDA treatment and incidence of pneumothorax.
- Infants ≤25 weeks GA requiring FiO₂ ≥ 0.3 are at risk of LISA failure
- Further studies are necessary to evaluate strategies to decrease LISA failure
- Need for MV in preterm infants can be decreased with concerted and sustained team efforts

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- All my Co-authors and leadership of UTSW- NPM division
- Parkland Resuscitation Team
- Parkland Golden Hour and CPAP/LISA team members
- All faculty, fellows, advanced practice providers and residents working/worked at Parkland NICU
- Research team and database management team



PAS Workshop, Denver, CO, 2022



PAS Workshop, Washington, DC, 2023



APLUS Conference, Dallas, TX, Oct 2023

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