Neonatal Resuscitation: Scientific Basis

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Children are Not Small Adults

Extremely preterm neonates are not small term babies

Babies are not small children

NRP vs. PALS

Credit: Martin Gradén/Volvo Car Corporation.
Evidence-Based Medicine vs. Physiologic Approach in Micro-preemies

**KATHERIA ET AL**
23-31 wk @ birth
- Umbilical cord milking (4 times) vs. delayed cord clamping (at least 60s)
- No difference in death
- Severe IVH more common in 23-27 wk subgroup with cord milking

**OEI et al**
< 32 wk @ birth
- Initiate resuscitation with 21% or 100% O₂ and titrate to target SpO₂
- No difference in mortality among all infants
- Higher hospital mortality with 21% O₂ initiation in < 28 wk gestational age group

**AUSTRALIAN PLACENTAL TRANSFUSION TRIAL**
< 30 wk @ birth
- Delayed cord clamping vs. immediate
- No difference in death or major morbidity by 36 weeks PMA

**SAIL TRIAL**
23-26 wk requiring PPV for inadequate respiratory effort or HR < 100 bpm
- Sustained Inflation vs. Intermittent PPV
- No difference in BPD or death @ 36 wk PMA
- Early death (< 48h)- more common in SI
Neonatal Resuscitation Algorithm—2015 Update

Physiology of Asphyxia

Room air vs. oxygen – term and preterm

Approach to Meconium Stained Amniotic Fluid (MSAF)

Targeted SpO2 with titrated FiO2

Mask ventilation

Chest compressions

Epinephrine

Targeted SpO2

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>SpO2 Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 min</td>
<td>60%–85%</td>
</tr>
<tr>
<td>2 min</td>
<td>65%–75%</td>
</tr>
<tr>
<td>3 min</td>
<td>70%–75%</td>
</tr>
<tr>
<td>4 min</td>
<td>75%–80%</td>
</tr>
<tr>
<td>5 min</td>
<td>80%–85%</td>
</tr>
<tr>
<td>10 min</td>
<td>85%–90%</td>
</tr>
</tbody>
</table>
Initial Questions to the Delivering Team

• **C**ord Management
• **L**ength of gestation (or Last Menstrual Period – LMP or EDD)
• **A**mniotic Fluid (Meconium, blood stained or clear)
• **S**ingle / Multiple gestation
• **P**redisposing factors
  • Maternal diabetes
  • Hypertension
Delayed – Duration > 30 sec

What should be the approach if resuscitation is needed?

Late-preterm and term infants, vaginal delivery non-breathing despite drying and stimulation for 30 s

Randomization

Early cord clamp (< 60s)

Delay cord clamp (≥ 180s)

Nepcord III (Andersson et al 2019) 5:15

Nurse-midwives trained in Helping Babies Breathe algorithm

Early first cry/breath and shorter time to regular breathing*

SpO2 at 1, 5 and 10 min*

Heart rate at 1, and 5 min*

Apgar at 1, 5 and 10 min*

No difference in baby’s temperature after resuscitation or bilirubin at discharge
Placental Transfusion

Intact cord milking

Milking 3 to 4 times in infants in need of resuscitation

Rapid bolus of 10-20 ml of blood
Umbilical cord milking

Uterine contractions

Placenta

Umbilical vein

PFO

Poor respiratory effort

↑ PVR and RV pressure

Umbilical venous milking ↑

LV preload

↑ carotid flow

Chorioamnionitis

Prematurity

↑ fragile blood vessels

↑ IVH

Pulm

Pulm artery

Umbilical arterial milking ↑ pressure in descending aorta

NO CORD MILKING IN EXTREMELY PRETERM INFANTS

Katheria et al PAS 2019
Placental Transfusion
Cut cord milking

Simultaneous initiation of resuscitation

Clamping away from the umbilicus

Long segment of the umbilical cord - milked by the neonatal resuscitator
Physiology of Asphyxia

Approach to Meconium Stained Amniotic Fluid (MSAF)

Room air vs. oxygen – term and preterm

Mask ventilation

Chest compressions

Epinephrine

Targeted SpO₂ with titrated FiO₂

Neonatal Resuscitation Algorithm—2015 Update

Physiological Approach

1. Term gestation? 
   - Yes
   - Term
   - Good tone? Breathing or crying?
   - Yes
   - Warm and maintain normal temperature, position airway, clear secretions if needed, dry, stimulate
   - No
   -窒息或气管插管?
   - Yes
   - No

2. Apnea or gasping? HR below 100/min?
   - Yes
   - No

3. HR below 100/min?
   - Yes
   - No

4. HR below 60/min?
   - Yes
   - No

5. Intubation if not already done
   - Chest compressions
   - Coordinate with PPV
   - 100% O₂
   - ECG monitor
   - Consider emergency shunt

6. HR below 60/min?
   - Yes
   - No

7. Epinephrine
   - IV epinephrine
   - If HR persistently below 60/min
   - Consider hypovolemia
   - Consider pneumothorax

Targeted SpO₂ After Birth

- 1 min: 60%-85%
- 2 min: 65%-70%
- 3 min: 70%-75%
- 4 min: 75%-80%
- 5 min: 80%-85%
- 10 min: 85%-95%

© 2010 American Heart Association
Changing Guidelines:
Suction Meconium – Vigorous vs. Non-vigorous

Hmmm...

Tangy......
### Metaanalysis – No Difference in Mortality/MAS

#### 1.1 Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>No ET suction</th>
<th>ET suction</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chettri et al</td>
<td>12</td>
<td>10</td>
<td>61</td>
<td>1.20 [0.56, 2.57]</td>
</tr>
<tr>
<td>Kumar et al.</td>
<td>5</td>
<td>9</td>
<td>66</td>
<td>0.56 [0.20, 1.57]</td>
</tr>
<tr>
<td>Nangia et al</td>
<td>4</td>
<td>9</td>
<td>88</td>
<td>0.44 [0.14, 1.37]</td>
</tr>
<tr>
<td>Singh et al.</td>
<td>7</td>
<td>4</td>
<td>77</td>
<td>1.70 [0.52, 5.58]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**
- Events: 292
- Total: 289
- Weight: 100.0%
- Risk Ratio: 0.87 [0.54, 1.40]

**Total events**: 28
**Heterogeneity**: Chi² = 4.02, df = 3 (P = 0.26); I² = 25%
**Test for overall effect**: Z = 0.58 (P = 0.56)
1.2 Meconium aspiration syndrome

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<th>No ET suction</th>
<th>ET suction</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
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<td>28</td>
</tr>
<tr>
<td>Singh et al</td>
<td>44</td>
<td>77</td>
<td>31</td>
</tr>
</tbody>
</table>

Total (95% CI) 292 289 100.0% 1.00 [0.70, 1.41]

Total events 101 100

Heterogeneity: Chi² = 5.94, df = 3 (P = 0.11) (I² = 50%)

Test for overall effect: Z = 0.02 (P = 0.98)
## TABLE 3 Neonatal Therapy and Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Denominator – non-vigorous babies with MSAF</th>
<th>OR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Retrospective (N = 130)</td>
<td>Prospective (N = 101)</td>
</tr>
<tr>
<td></td>
<td>Routine Tracheal Suction</td>
<td>No Routine Tracheal Suction</td>
</tr>
<tr>
<td>NICU respiratory admissions&lt;sup&gt;b&lt;/sup&gt;</td>
<td>29 (22)</td>
<td>40 (40)</td>
</tr>
<tr>
<td>Oxygen therapy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24 (19)</td>
<td>37 (37)</td>
</tr>
<tr>
<td>Mechanical ventilation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11 (9)</td>
<td>19 (19)</td>
</tr>
<tr>
<td>Surfactant therapy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (2)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Inhaled nitric oxide therapy</td>
<td>3 (2)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Hypothermia therapy</td>
<td>4 (3)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>MAS</td>
<td>7 (5)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>HIE</td>
<td>5 (4)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Transfer for ECMO</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for late preterm, postterm, and deliveries with fetal distress.

<sup>b</sup> P < .05.
Meconium stained amniotic fluid 10-15% of deliveries

No stimulation of all ‘visibly appearing’* non-vigorous newborns (10-20%)

Dry and stimulation of all newborns by obstetric or neonatal providers

Vigorous following stimulation*

Vigorous without stimulation

Initial non-vigorous state (10-20%)

How can we measure incidence of Meconium Aspiration Syndrome (MAS)?

Persistent non-vigorous state (8-10%)

Move to positive pressure ventilation (PPV)

Problems of decreasing denominators

Routine tracheal intubation and suction

Larger denominator with some well newborns

Smaller denominator with sicker newborns

*May include newborns who briefly visibly appeared non-vigorous
### Vermont Oxford Network - ≥ 35 w GA + Meconium Aspiration syndrome + Apgar Score < 3 at 1 min

<table>
<thead>
<tr>
<th></th>
<th>2013-15</th>
<th>2017</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Births</strong></td>
<td>N=222,438</td>
<td>N=78,712</td>
<td></td>
</tr>
<tr>
<td><strong>MAS with Apgar &lt; 3 at 1 min</strong></td>
<td>N=1586</td>
<td>N=362</td>
<td></td>
</tr>
<tr>
<td>Endotracheal suctioning, %</td>
<td>82.4</td>
<td>52.1</td>
<td>0.63 (0.56, 0.71)</td>
</tr>
<tr>
<td>Conventional or high frequency ventilation, %</td>
<td>57.4</td>
<td>61.9</td>
<td>1.08 (0.97, 1.20)</td>
</tr>
<tr>
<td>Inhaled nitric oxide, %</td>
<td>16.2</td>
<td>21.9</td>
<td>1.35 (1.08, 1.69)</td>
</tr>
<tr>
<td>ECMO, %</td>
<td>1.8</td>
<td>2.3</td>
<td>1.23 (0.47, 3.19)</td>
</tr>
<tr>
<td>Surfactant at any time, %</td>
<td>27.7</td>
<td>36.0</td>
<td>1.30 (1.09, 1.55)</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, %</td>
<td>5.3</td>
<td>7.2</td>
<td>1.38 (0.88, 2.16)</td>
</tr>
<tr>
<td>Pneumothorax, %</td>
<td>10.3</td>
<td>11.5</td>
<td>1.11 (0.80, 1.55)</td>
</tr>
<tr>
<td>Moderate/severe hypoxic-ischemic encephalopathy, %</td>
<td>12.1</td>
<td>20.1</td>
<td>1.67 (1.27, 2.19)</td>
</tr>
</tbody>
</table>

Edwards E et al Children 2019
The current “no routine suction” recommendation has not led to increased ECMO for MAS.
Treatment Recommendations – ILCOR 2019 (Consensus on Science with Treatment Recommendations (CoSTR))

• For non-vigorous newborns delivered through meconium-stained amniotic fluid, we suggest against routine immediate direct laryngoscopy after delivery with or without tracheal suctioning when compared to immediate resuscitation without direct laryngoscopy.

• Meconium-stained amniotic fluid remains a significant risk factor for receiving advanced resuscitation in the delivery room.

• A provider may perform intubation and tracheal suctioning to relieve airway obstruction.
What is Optimal Oxygenation in the Delivery Room?
Term: Effects of Resuscitation with 100% O₂

Diagrammatic Representation

- 100% O₂ PaO₂
- Brain inflammation ↑HIE
- Myocardial damage
- Acute renal injury
- ↑ Mortality
- 100% O₂ free radicals
- Childhood leukemia
- 21% O₂ PaO₂
- 21% O₂ free radicals

Timeline:
- Fetus Birth 1
- 5
- 10 min
- 7d
- 14d
- 28d
- Childhood

Slide courtesy: Dr. Saugstad
What about Preterm Infants?

Saugstad et al. Pediatric Research 2018

Oei JL et al. Arch Dis Child Fetal Neonatal Ed 2018


Low SpO₂ and heart rate @ 5 min - risk of IVH and death

Closed glottis and epiglottis

Immature fluid-filled lungs in canalicular stage

Surfactant deficiency

Poor pulmonary vascular transition and respiratory failure

Mask leaks

Need for higher pressures due to poor compliance

Low alveolar PAO₂

Airspace-capillary interphase poorly developed

Lower PaO₂

Pulmonary vascular smooth muscle less responsive to O₂, endogenous NO and other vasodilators
What is Optimal Oxygenation in the Delivery Room?

Delivery room
> 31 weeks: air
28-31 weeks: air or 30%
< 28 weeks: 30%
At 5 min: SpO₂ ≥ 80% and HR > 100 bpm

ILCOR – CoSTAR treatment guidelines:

We suggest starting with a lower oxygen concentration (21-30%) compared to higher oxygen concentration (60-100%) for preterm (<35 weeks gestation) newborns who receive respiratory support at birth with subsequent titration of oxygen concentration using pulse oximetry (weak recommendation, very low certainty of evidence).
Corrective Steps – MRSOPA

1. M - Adjust MASK to assure good seal on the face

2. R - REPOSITION airway by adjusting head to sniffing position

3. S - SUCTION mouth and nose of secretions (if present)

4. O - OPEN mouth slightly and move jaw forward

5. P - PRESSURE - increase pressure to achieve chest rise

6. A - Consider AIRWAY alternative endotracheal intubation or laryngeal mask airway
Intubation - ETT

I am sure the tube is in.

It is still purple..

Low inadequate PIP to open alveoli

Low ventilation

Inadequate tidal volume

Obstruction

Hypoplastic alveoli

Stiff poorly compliant lungs

Hypoplastic arterial PCO2

Pulmonary arterial PCO2

Severe PPHN

Alveolar PCO2

Persistent purple color (no change in colorimetric CO2 detection device)

Misplacement (in the esophagus)

Low Qp

Cardiac dysfunction (or arrest)

Atmospheric PCO2 - low levels

↑ HR
Physiology of Asphyxia

Neonatal Resuscitation Algorithm—2015 Update

Approach to Meconium Stained Amniotic Fluid (MSAF)

Room air vs. oxygen – term and preterm

Mask ventilation

Chest compressions

Epinephrine

Targeted SpO₂ with titrated FiO₂
• Intravenous (UV) administration of epinephrine may be considered at a dose of 0.01 to 0.03 mg/kg of 1:10,000 epinephrine followed by 0.5 to 1 ml of flush.

• If an endotracheal administration route is attempted while intravenous access is being established, higher dosing will be needed at 0.05 to 0.1 mg/kg.
ETT Epinephrine

- Dilution by fetal lung fluid
- Endotracheal epinephrine administration
- Diffusion barrier
- Low pulmonary blood flow (poor absorption)
- High PVR

1. Right to left shunt across foramen ovale
2. Coronary artery
3. Ductus venosus

UVC Epi
- Plasma Epi concentration ng/ml
- UVC Epi
  - 0.03 mg/kg

ETT Epi DR
- Postnatal (NICU)
- 0.1 mg/kg
- 0.1 mg/kg

Nair et al Early Hum Dev 2019
Newly born in the DR
Slow absorption – reservoir effect

Postnatal in the NICU – higher levels

Lung liquid dilutes epinephrine and limits absorption
Endotracheal epinephrine administration
Poor compliance and diffusion barrier limit absorption

Air filled lung enhances epinephrine absorption
Endotracheal epinephrine administration
Improved compliance and better diffusion

0.1 mg/kg dose
X 1 only

0.05 mg/kg dose
X 1 only

Nair et al Early Hum Dev 2019
Current Recommended Flush – 0.5 to 1 ml

Volume of a 5 Fr single lumen UVC is 0.56 ml

Potential Benefit Of Higher Flush Volume

- High Intrathoracic Pressure – PPV and CC
- Absence of spontaneous cardiac activity
- Low UVC
- Umb vein
- Higher flush volume
- Epinephrine
Distribution Of Epinephrine

A. Epinephrine followed by 1 ml contrast (Omnipaque) flush + 30 sec of chest compressions

B. Epinephrine followed by 10 ml contrast (Omnipaque) flush + 30 sec of chest compressions
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low dose (0.01 mg/kg) n=11</th>
<th>High dose (0.03 mg/kg) n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low flush (6)</td>
<td>High flush (5)</td>
</tr>
<tr>
<td>ROSC achieved n(%)</td>
<td>2 (33%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>ROSC with 1\textsuperscript{st} dose of epi</td>
<td>1 (16.7%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Median time to ROSC from PPV (sec)</td>
<td>697 (536-858)(^\wedge)</td>
<td>397 (396-398)</td>
</tr>
<tr>
<td>Median time to ROSC from epi &amp; flush (sec)</td>
<td>127 (101-153)(^\wedge)</td>
<td>90 (60-120)</td>
</tr>
</tbody>
</table>

ROSC: Return of Spontaneous Circulation
\(^\wedge\) p<0.05 low dose low flush vs high dose high flush. (unpaired t test)
\(\dagger\) p<0.05 high dose high flush vs low dose low flush

Sankaran et al PAS 2019
### Parameters

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<th>High dose</th>
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<tbody>
<tr>
<td>Dose</td>
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<td>0.03 mg/kg</td>
</tr>
<tr>
<td>n</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td><strong>ROSC achieved</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ROSC with 1st dose of epi</strong></td>
<td>1 (16.7%)</td>
<td>2 (40%)</td>
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<td><strong>ROSC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to ROSC from PPV (sec)</td>
<td>697 (536 - 858)</td>
<td>397 (396 - 398)</td>
</tr>
<tr>
<td>Median time to ROSC from epi &amp; flush (sec)</td>
<td>127 (101 - 153)</td>
<td>47 (41 - 53)</td>
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</tbody>
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*ROSC: Return of Spontaneous Circulation*  

[^p<0.05 low dose low flush vs high dose high flush. (unpaired t test)](Sankaran et al PAS 2019)  

[^†p<0.05 high dose high flush vs low dose low flush]  

Dose – 0.03 mg/kg or 0.3 ml/kg 1:10,000

↓

Flush – 3 ml/kg

(~10 ml in Term)
Summary

- Ventilation of the lungs is the key to neonatal resuscitation
- Increasing heart rate is the most important sign of effective resuscitation
- Avoid cord milking in extremely preterm infants
- 21% oxygen may not be adequate for initial resuscitation of extremely preterm infants
- Epinephrine: avoid multiple ET doses
- UVC epinephrine: 0.03mg/kg → 3 ml/kg flush
1. Cleaning and cutting the umbilical cord

2. Sterile, flushed umbilical venous catheter inserted after dilating the umbilical vein

3. Syringe with appropriate dose of epinephrine administered through the umbilical venous catheter

4. Umbilical venous catheter flushed with normal saline to propel epinephrine to the neonate's heart

Direct UV EPI

1. Epinephrine 1:10,000 0.03 mg/kg injection into umbilical vein at the base of the umbilical cord

2. Cut-umbilical cord (20 cm segment) Milk x 3 to flush epinephrine

Ductus venosus