Hot topics of ongoing research that are likely to come into clinical use in the next 5 years?

Can We Hope For A Better Tomorrow?

SRMC 11th March 2017

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St. John’s Medical College, Bengaluru
Disclaimer

- I am not an Astrologer
- This is my BEST GUESSTIMATE!
- GOK.....
- This is totally BIASED by my interests!
Overview

- Delivery room interventions
- Asphyxia
- Interventions for preterm
- Sepsis
- USG
- QI
- Innovations
Causes of Neonatal Mortality

- Prematurity
- Sepsis
- Asphyxia
Delivery Room Interventions

- SI
- Placental transfusion
- ET
Sustained Inflation
Cochrane Meta-analysis

- 2 trials enrolling 352 infants
- Mortality: RR 1.59, 95% CI 0.81 to 3.10
- Intubation < 72 h: RR 0.85, 95% CI 0.72 to 1.02
- Chronic lung disease: RR 1.06, 95% CI 0.79 to 1.42
- Not a recommendation

SLI RCT

- 291 infants < 29 weeks
- Need for mechanical ventilation 53% Vs 65%
- BPD similar
- Air leaks increasing trend
- Routinely used in ELGAN – Germany

Lista, et al. the SLI Trial Investigators. Sustained Lung Inflation at Birth for Preterm Infants: A Randomized Clinical Trial. Pediatrics 2015; 135
SAIL - Sustained Aeration of Infant Lungs

- Multisite prospective randomized controlled unblinded trial
- 600 infants of 23 - 26 wks GA with respiratory support at birth.
- Intervention SI (20 cm H$_2$O for 15 seconds) followed by a second SI (25 cm H$_2$O for 15 seconds), and then PEEP + IPPV
- Control group - initial IPPV with PEEP.
- Primary outcome is the combined BPD / death at 36 weeks post-menstrual age.

*Foglia et al. Sustained Aeration of Infant Lungs (SAIL) trial: study protocol for a randomized controlled trial* Trials. 2015; 16: 95
Placental transfusion
Placental transfusion by delayed cord clamping is recommended in both term and preterm neonates who do not require resuscitation (AAP NRP update 2015 and WHO 2014)

Benefits of placental transfusion in preterm neonates are many and in particular there is reduction in IVH, NEC and need for transfusion (Cochrane 2012)

Neonates requiring resuscitation are currently deprived of the benefits of placental transfusion (Cochrane 2012)
Placental Transfusion

- C- UCM – Cut Umbilical Cord Milking
- NRIC – Neonatal Resuscitation on Intact Cord

Total preterm deliveries (n=542)

Approached for consent (n=211)

Excluded (n=151)
- Did not require resuscitation (n=82)
- Multiple births (n=36)
- Rh negative pregnancy (n=21)
- Refused to participate (n=8)
- Missed (n=4)

Did not require resuscitation (n=82)

Multiple births (n=36)

Rh negative pregnancy (n=21)

Refused to participate (n=8)

Missed (n=4)

Randomized (n=60)

Milking (n=30)
- Received allocated intervention (n=30)

Lost to follow up (n=0)

Analyzed (n=30)

No milking (n=30)
- Received allocated intervention (n=30)

Follow up
- death (n=2)
- Lost to follow up (n=0)

Analysis
- Analyzed (n=28)
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cord milking group (n=30)</th>
<th>No milking group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)*</td>
<td>32.7± 2.4</td>
<td>32.4 ± 2.2</td>
</tr>
<tr>
<td>Birth weight (g)*</td>
<td>1596.3±612.4</td>
<td>1465.0±342.7</td>
</tr>
<tr>
<td>AGA#</td>
<td>28 (93.3%)</td>
<td>25 (83.3%)</td>
</tr>
<tr>
<td>SGA#</td>
<td>1 (3.3%)</td>
<td>5 (16.6%)</td>
</tr>
<tr>
<td>Male sex #</td>
<td>21 (70)</td>
<td>17 (56.6)</td>
</tr>
<tr>
<td>Caesarean delivery #</td>
<td>24 (80%)</td>
<td>28 (94%)</td>
</tr>
<tr>
<td>Apgar score at 5 min$</td>
<td>8 (8-8)</td>
<td>8 (7-8)</td>
</tr>
<tr>
<td>Adequate antenatal steroids #</td>
<td>16 (53.3%)</td>
<td>15 (50%)</td>
</tr>
<tr>
<td>Intrapartum fever #</td>
<td>3 (10%)</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>CRIB score*</td>
<td>1.2±1.07</td>
<td>1.3±0.99</td>
</tr>
</tbody>
</table>

*mean and standard deviation (SD)  
# number (percentages shown in parentheses)  
$ Median and interquartile range
Primary Outcome: Hb @ 6 wks

S. Ferritin @ 6 wks

HCT on Day 1

MAP < 6 h
Other Outcomes

- Sepsis
  - Milking: 1
  - No milking: 5

- Packed cell transfusion
  - Milking: 3
  - No milking: 6
Feasibility study – observational

Six infants

GA – 31 (30-36) wks

Birth weight 1655g (1380-2650),

4 received CPAP on iNSPiRe

Thomas et al. Integrated Neonatal Support on Placental circulation with Resuscitation (iNSPiRe)” A feasibility study. 6th World Pediatric Congress August 18-19, 2016 Sao Paulo, Brazil
Resuscitation on Placental Support

- NRIC – Neonatal Resuscitation on Intact Cord
- INSPIRe / LifeStartP
- CLD, IVH
- Mobile battery powered resuscitation platform
- Warm gel mattress

NRIC
Other Delivery Room Trials

- Modified Tochen Formula - St. Johns
- LMA Vs Face Mask - For PPV
- HeLP trial – Heat loss prevention trial
To Cool or Not!
**Cochrane Meta-analysis – Jacobs et al 2013**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hypothermia n/N</th>
<th>Standard care n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Selective head cooling with mild systemic hyperthermia</td>
<td>7/18</td>
<td>4/13</td>
<td></td>
<td>1.1%</td>
<td>1.26 [0.46, 3.44]</td>
</tr>
<tr>
<td>Cool Cap Study 2005</td>
<td>59/108</td>
<td>73/110</td>
<td></td>
<td>17.6%</td>
<td>0.82 [0.66, 1.02]</td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>31/100</td>
<td>46/94</td>
<td></td>
<td>11.5%</td>
<td>0.63 [0.44, 0.91]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td><strong>226</strong></td>
<td></td>
<td><strong>217</strong></td>
</tr>
<tr>
<td><strong>Total event:</strong> 57 (Hypothermia), 123 (Standard care)</td>
<td></td>
<td></td>
<td><strong>30.3%</strong></td>
<td></td>
<td><strong>0.77 [0.64, 0.92]</strong></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Chi² = 2.46, df = 2 (P = 0.29); I² = 19%
Test for overall effect: Z = 2.78 (P = 0.0054)

2 Whole body cooling

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypothermia n/N</th>
<th>Standard care n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Weight</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Eichler 2005</td>
<td>14/27</td>
<td>21/25</td>
<td></td>
<td>5.3%</td>
<td>0.62 [0.41, 0.92]</td>
</tr>
<tr>
<td>NICHD Study 2005</td>
<td>45/102</td>
<td>64/103</td>
<td></td>
<td>15.5%</td>
<td>0.71 [0.54, 0.93]</td>
</tr>
<tr>
<td>TOBY Study 2009</td>
<td>74/163</td>
<td>86/162</td>
<td></td>
<td>21.0%</td>
<td>0.86 [0.68, 1.07]</td>
</tr>
<tr>
<td>n.euroEURO Study 2010</td>
<td>27/53</td>
<td>48/58</td>
<td></td>
<td>11.2%</td>
<td>0.62 [0.46, 0.82]</td>
</tr>
<tr>
<td>ICE Study 2011</td>
<td>55/107</td>
<td>67/101</td>
<td></td>
<td>16.8%</td>
<td>0.77 [0.62, 0.98]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td><strong>452</strong></td>
<td></td>
<td><strong>449</strong></td>
</tr>
<tr>
<td><strong>Total event:</strong> 521 (Hypothermia), 286 (Standard care)</td>
<td></td>
<td></td>
<td><strong>69.7%</strong></td>
<td></td>
<td><strong>0.75 [0.66, 0.84]</strong></td>
</tr>
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**Heterogeneity:** Chi² = 5.26, df = 4 (P = 0.37); I² = 6%
Test for overall effect: Z = 4.80 (P < 0.00001)

**Total (95% CI)**

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<tr>
<th>Study</th>
<th>Hypothermia n/N</th>
<th>Standard care n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
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<tr>
<td><strong>678</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>0.75 [0.68, 0.83]</strong></td>
</tr>
</tbody>
</table>

**Total events:** 312 (Hypothermia), 409 (Standard care)

**Heterogeneity:** Chi² = 3.65, df = 7 (P = 0.44); I² = 0.0%
Test for overall effect: Z = 3.52 (P < 0.00001)

**Disability in survivors (18 mo)**

<table>
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**MRI abnormalities**

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<tbody>
<tr>
<td><strong>RR: 0.73; 95% CI 0.6 - 0.89</strong></td>
<td></td>
<td></td>
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</table>

**Outcome:** 1 Death or major disability in survivors assessed, by method of cooling

**Comparison:** 1 Therapeutic hypothermia versus standard care; subgroup analysis by method of cooling

**Review:** Cooling for newborns with hypoxic ischemic encephalopathy

**RR:** 0.75; 95% CI 0.68-0.83

**Mortality**

**RR:** 0.75; 95% CI 0.64-0.88

**Disability in survivors (18 mo)**

**RR:** 0.67; 95% CI 0.55-0.80
Meta-analysis - LMIC

Mortality - cooled vs non-cooled


"Cooling therapy - No reduction in mortality in LMIC"

"Evaluation of safety & efficacy of cooling in adequately powered RCTs is reqd before cooling is offered in routine clinical practice in LMIC"

Why LMIC result is different?

- Latent period lost - Onset of asphyxia
- Malnutrition, chronic in utero hypoxia, late seeking of care, obstructed labor
- Sub optimal NICU care
- Infections
- Accidental hypothermia

Hypothermia for Encephalopathy in low and middle income countries

- Temp - 33.5°C < 6 h for 72 h
- Sample - 408 babies
- Intervention – Therapeutic hypothermia
- Method of cooling – Tecotherm
- Outcome – Death / disability at 18 months
- MR imaging and spectroscopy at 1 week
HELIX - Hypothermia for Encephalopathy in low and middle income countries

Participating sites

- Madras Medical College, Chennai
- Sion Hospital, Mumbai
- Indira Gandhi Hospital, Bangalore
- Calicut Medical College, Kerala.
- MAMC, New Delhi
Therapeutic Hypothermia +

- Necrostatin
- Epo
- Melatonin
- MgSO₄
- Inflammation
- Repair
- Allopurinol
- Oxidative stress
- Excitotoxicity

1. Magnesium
2. Xenon
3. Erythropoietin
4. Stem Cells
5. NAC
6. Melatonin
7. Anticonvulsants
8. Antioxidants
8a. Allopurinol
9. BH₄
10. Hydrogen Sulfide
Hypothermia +

- Xenon
- EPO / Darbepoietin
- Autologous cord blood
- UCM
- Inhalative $\text{CO}_2$ (HENRIC)
- Clonidine
- Melatonion
- Hyperbaric oxygen
- Sildenafil
- (IUGR - DUTCH STRIDER study)
Which Anticonvulsant?

- When can we stop?
- How long to continue?
- Effect of long term therapy
  - No Pb maintenance (CTRI)
Total babies Randomized
n = 38 (all cause seizures)

Levetiracetam n = 20

Phenobarbitone n = 18

Need for other drug n = 6

Levetiracetam Vs Pb – SJMCH Study
Levetiracetam

- Multicentric study 2015 to 2020
- 100
- Levetiracetam Vs Phenobarbitone.
- EEG/ BSID
- Pharmacokinetic component

https://www.clinicaltrials.gov/ct2/home
Interventions for the Preterm
Goat Lung Surfactant Trial

- Active controlled RCT, non inferiority trial
- Multicentric trial – 12
- Subjects < 32 weeks, < 6 h, CPAP >0.4 FiO\(_2\) / intubated
- No. of subjects - 900
- Outcome: BPD free survival
- Rs. 1000 surfactant
Respiratory Trials

- Early Vs late caffeine
- < 24 h Vs > 24 h
- BPD

- Hydrocortisone for BPD

- Frusemide in “at risk BPD”

- Pneumostem (stem cells for BPD)

https://www.clinicaltrials.gov
Ventilation Trials

- SNIPPV (NAVA) Vs CPAP
- BPD; 60
- NAVA Vs PA
- Cross over; OI
- RAM cannula
- IN-REC-SUR-E
- HFV recruitment maneuver
Management of Hypoglycemia
Sugar Baby Study

- At risk with hypoglycemia - IDM, preterm
- Oral dextrose gel
- Reduces treatment failure (blood sugar < 2.6 mmol/L).

16 [14%] vs 29 [24%]; relative risk 0.57, 95% CI 0.33-0.98; p=0.04.

Cochrane Meta-analysis 2016

- Rx of Neonatal hypoglycaemia with 40% dextrose gel
- Mother-infant separation for treatment
- Increases the likelihood of full breast feeding

Dextrose gel should be considered for first-line treatment to manage hypoglycaemia in late preterm and term babies in the first 48 h after birth.
Hypoglycemia Prevention by Oral Dextrose

Aims at recruiting 2129 babies AT RISK for hypoglycemia

40% dextrose gel given to babies at risk

Outcomes:

- Admission to Neonatal Intensive Care
- Neurosensory outcome

Harding et al. Randomised trial of neonatal hypoglycaemia prevention with oral dextrose gel (hPOD): study protocol. BMC Pediatr. 2015 Sep 16;15:120
Feed

- Oropharyngeal colostrum: LOS/ NEC/VAP: > 600 neonates
- Frequency of feeding (Q2 H to Q3 H)
- SIFT – Speed of increasing milk feeds trial / PGI
- SUPP – Glycerine suppository used prophylactically for preterm
- STP206 for NEC
Preterm infants on early solid feeds (PIES Trial)

- 10-12 wks Vs 16-18 wks (O: ht @1 y)
- AIIMS - 4th mo Vs 6th mo (O: wt Z scores, DXA)

Omega 3

- BPD (MOBYDick), ROP, NDO
- Deep placental disorders
Anemia

TOP study – Transfusion Of Prematures – NICHD trial

- <1000 g / <29 wks
- Liberal Transfusion Vs Restricted Transfusion
- Death/ NDO
- Cerebral oxygenation & NIRS
- Can it predict abn NDO?
ROP

- Propranolol
- DROP – ROP 0.2%; Stage I
- Oral; Stage 2
- Omega ROP
- Prevention

Shock

- Management of Shock
- Dopamine Vs Adrenaline
- Early hydrocortisone
**Early SCC for 28-32 weeks**

- Norwegian study
- Immediately after birth – max 2 h
- NDO- BSID
- GM

**Antibiotic Stewardship**

- Those at low risk
- 3 arms- Ab/ placebo/ physician choice
- Study of microbiome and clinical
Family Centred / Integrated Care
CKMC-DEV Study

- Community Kangaroo Mother Care for Improving Child Survival and Brain Development in Low Birth Weight Newborns (CKMC-DEV)
- 40% home delivery or < 12 hours discharge
- Outcome measures – BSID, maternal depression, competence, bonding, temperament
Neonatal Sepsis Mx
SES – Syndrome Evaluation System

- Multiplex PCR based molecular diagnostic method.
- A RCT - 385 neonates - two groups -- SES and control (BACTEC)
- Diagnosis - (68 % vs. 18 % SES gp; 72 % vs. 18 % control gp)
- Outcome : 100 % concordance with BACTEC
  - Rapid (7 h vs. 72 h)
  - Lower mortality (3 % vs. 18 %), hospital stay and change in antibiotics

_Bhat et al. SES Vs Bactec in the diagnosis and management of Neo sepsis – A RCT. Indian J Pediatr 2016;83:370-9_
7 days antibiotics Vs 14 days

- Non inferiority RCT
- Multicentric – 700 babies
- Blood culture +, uncomplicated sepsis
- Clinical remission by D5 of IV Ab
- Excl: staph, meningitis, arthritis, OM, abscess
Community management of Neonatal Sepsis

African Neonatal Sepsis Trial group

- Open labeled equivalence trial
- Young infants with fast breathing
- Oral amoxicillin Vs penicillin-gentamicin
Point of Care USG

USG - The New Stethoscope
USG Beyond NSG / ECHO
Fig. 15. Surfactant deficiency disease. (A) Chest radiograph of a preterm infant shows diffuse granular airspace disease typical of surfactant deficiency, worst in the right lower lobe. (B) Transverse sonogram of the right lower chest through the liver (L) shows abnormal increased pulmonary echogenicity of the right lower lobe without visualization of focal B lines.
Ongoing Trial

- Clearance of lung fluid
- Prediction of need of respiratory support / surfactant
Lines....Intubation , LP
Quality Improvement in NICU

The New Mantra
"Knowing is not enough; we must apply. Willing is not enough; we must do."

–Goethe
QI – Not a choice any more!

Desirable ➔ Mandatory

- Public display of outcome
- Pay for Performance
- No insurance cover for complications
What are we hoping to accomplish?

How will we know that a change is an improvement?

What changes can we make that will result in an improvement?

1992 - Langley 's Model of Improvement
“Systematic data guided activities designed to bring out immediate improvements in health care delivery in a particular setting”

Is QI Research?

Hastings Centre Report

<table>
<thead>
<tr>
<th>Research</th>
<th>Quality Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Discover new knowledge</td>
<td>• Apply current knowledge</td>
</tr>
<tr>
<td>• One test - takes long time</td>
<td>• Multiple short test cycles</td>
</tr>
<tr>
<td>• Subjects often do not benefit</td>
<td>• Subjects likely to benefit</td>
</tr>
<tr>
<td>• As much data as possible</td>
<td>• Data is contextual &amp; minimal</td>
</tr>
<tr>
<td>• Randomized, blinded, control gp, funded, published</td>
<td>• X randomised, blinded, control group, X funded. X published</td>
</tr>
<tr>
<td>• Frequent feedback to modify behavior</td>
<td>• Delays feedback to prevent bias</td>
</tr>
<tr>
<td>• Requires informed consent</td>
<td>• Recommend general notice to families</td>
</tr>
<tr>
<td>• Ignores NICU culture</td>
<td>• Seeks integration to NICU culture</td>
</tr>
<tr>
<td>• Opinions of non study pers. irrelevant</td>
<td>• Opinions of non study personnel vital</td>
</tr>
<tr>
<td>• More than routine risk</td>
<td>• Routine risk</td>
</tr>
<tr>
<td>• IRB review</td>
<td>• Review by clinical management Team</td>
</tr>
<tr>
<td>• Knowledge applicable to many sites</td>
<td>• Results mostly applicable to single site</td>
</tr>
</tbody>
</table>
Breast Milk Quality Improvement Bundle For VLBW Babies

Akhasha M. Mogha, Saradini Nesargi, Suman Rao
Department of Neonatology, St. John's Medical College and Hospital, Bangalore, India.

Presentations
Prizes
Publications
> 1 lakh
1862 newborn
Implementation Research

WHO - GATES PROJECT
Goal – 80% coverage

- Koppal KMC
- AKKA Model
- Association of KMC Kare Activists
- KMC Chain
Innovations

- MR Scanner Capable of Being Sited in a Neonatal Intensive Care Unit

- (Firefly Sheffield)

https://www.clinicaltrials.gov/ct2/home
Remote Bio Monitoring Tool
Conceptual framework for RBM device

1. Wearable device (mother + newborn)

2. Gateway device / smartphone

3. Cellular network

4. Data analytics

5. Data feedback
RBM Data

Temperatures and Skin contact (neonatal & maternal) during no KMC period (Neonate 2) -- no direct observation

- Baby's temp
- Mothers Temp
- Baby touch
- Mother touch
Saans
Flow / Power independent CPAP

Features

- No Expert Needed
- No Power Source
- Constant Pressure
- Constant Flow
- Filtered Air
Key Messages

- Many many ongoing trials
- Relevant for India
  - Prematurity
  - Asphyxia
  - Infections
- QI – Bridge the know-do gap