Therapeutic hypothermia – Are we ready?

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Are we ready?

Depends!

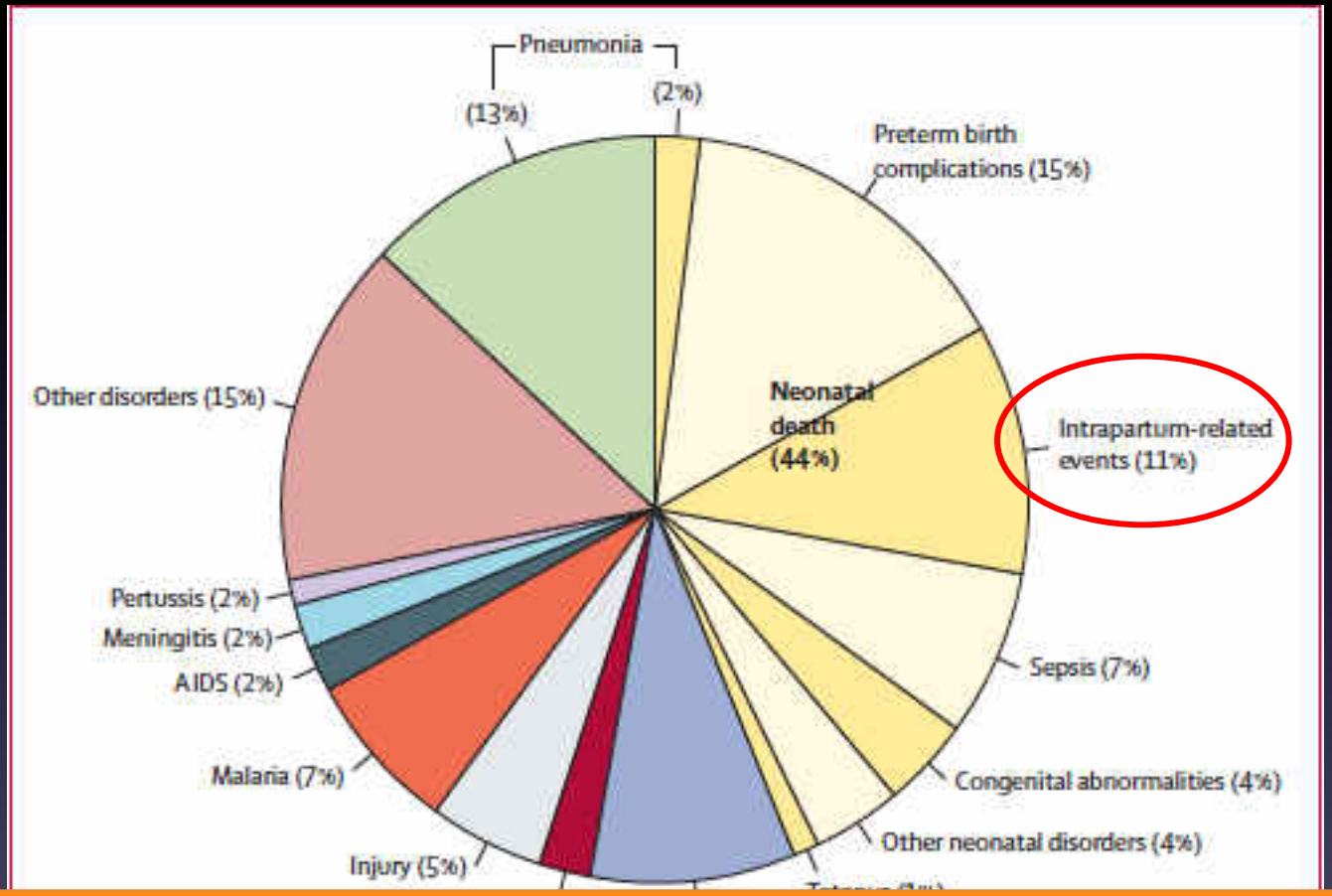
Are we ready?

Questions

1. Why?
   - Science, evidence
2. Why not?
   - Practical difficulties, cost, …
3. Should we?
   - Balance between why & why not?
4. How?
   - Solutions

Why?

Causes of child deaths



2nd common cause of neonatal deaths!

Liu, Lancet 2015

Asphyxia – Management

Intervention	No. of studies	Type of Study	No. of infants	Long-term outcome	Conclusion
Magnesium sulfate	1 1	Safety RCT	15 33	N.A N.A	Higher dose: Hypotension; low dose: Resp. depression can occur Better short term outcomes (CT scan, EEG and oral feeds by 14 days)
Allopurinol	1 1	RCT Systemic Review	22	? Available	No difference in the mortality & long-term outcome Insufficient evidence
Calcium channel blockers	1	Case-series	4	N.A	No RCTs so far

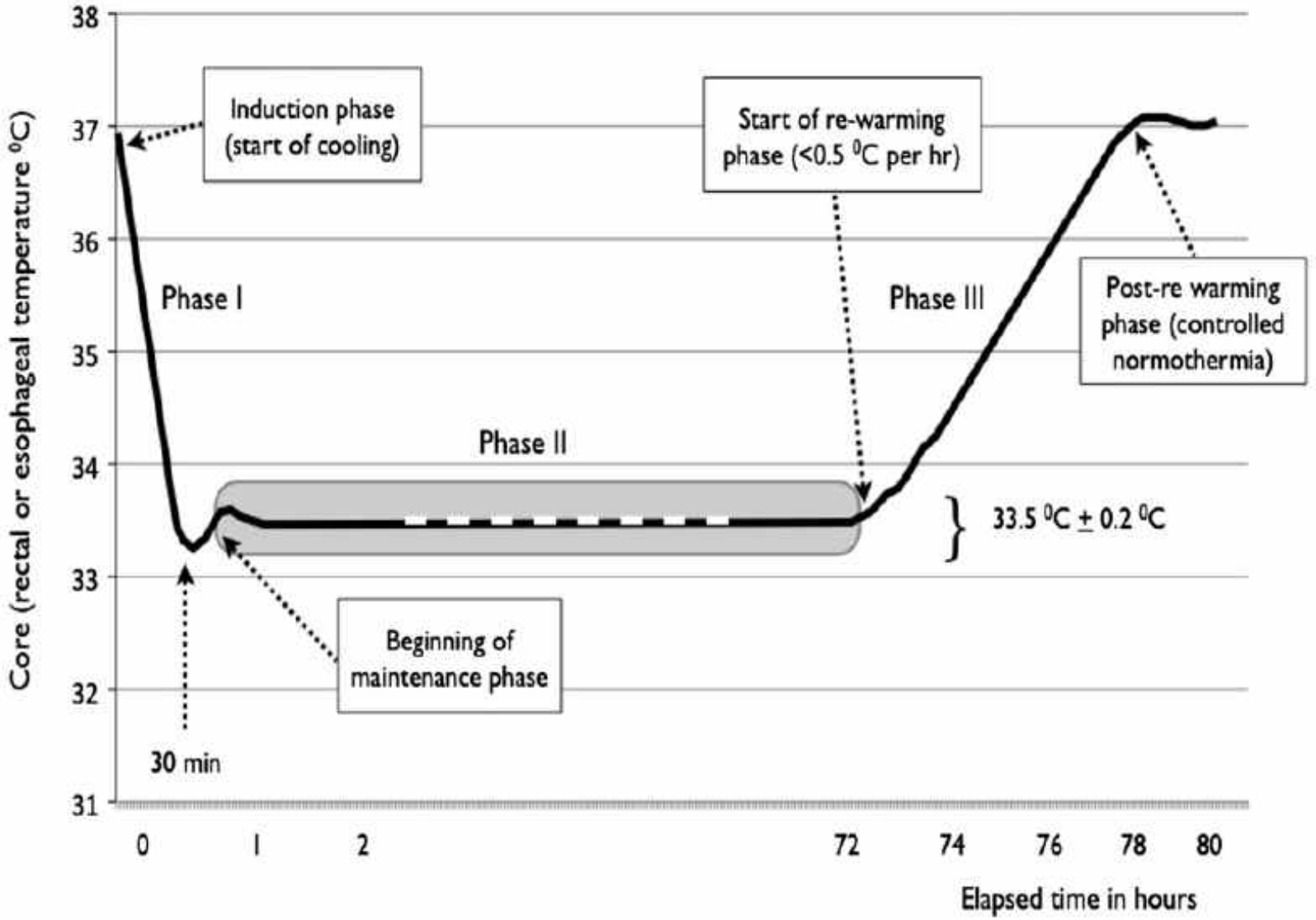
Asphyxia – Management

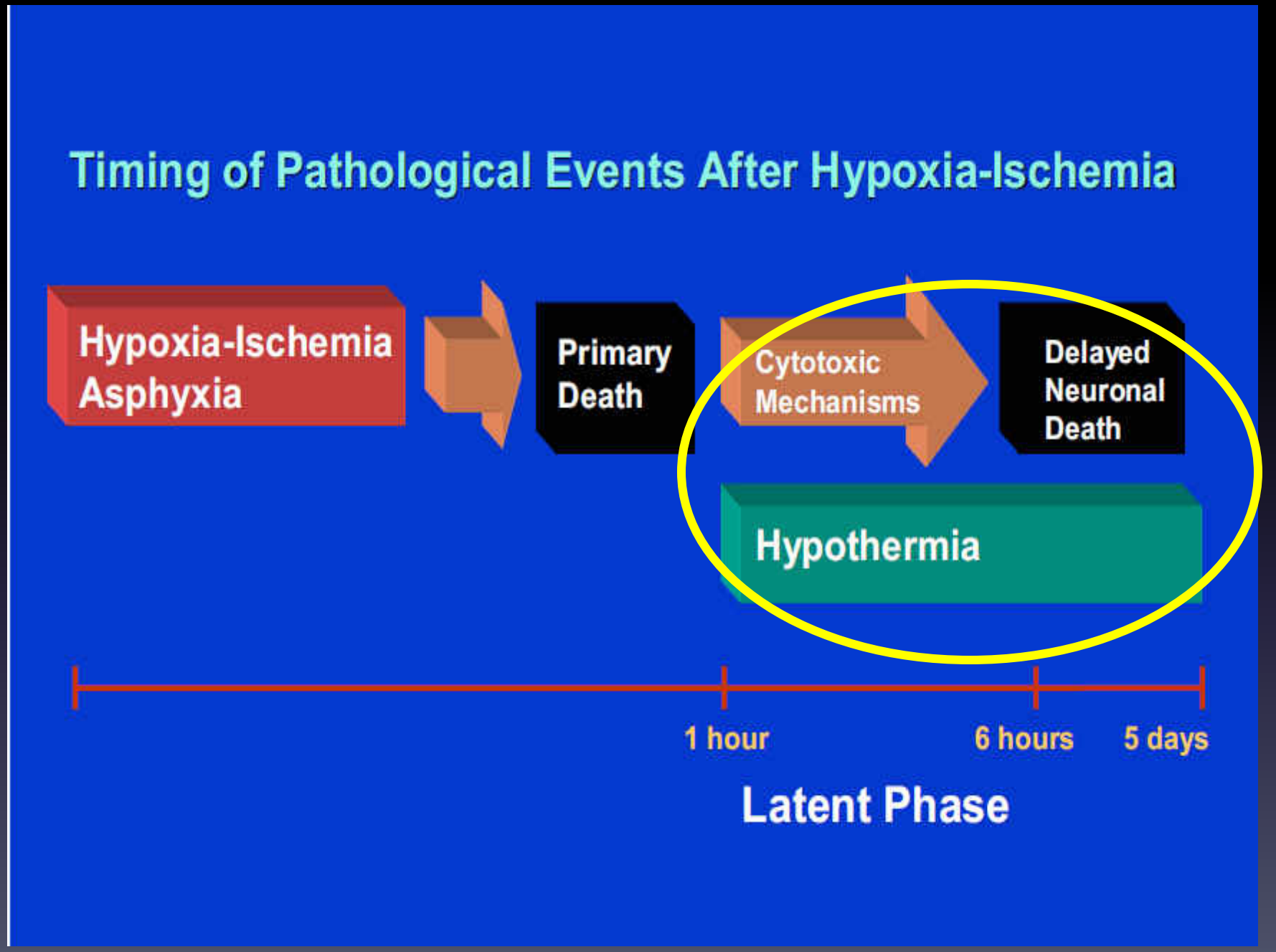
Intervention	No. of studies	Type of Study	No. of infants	Long-term outcome	Conclusion
Steroids	1	Case-series	?	N.A	No effects on cerebral perfusion pressure
Mannitol	1	RCT	25	N.A	No difference in the mortality
Opiate antagonists	1 1	RCT Cochrane	193	N.A	No difference in HR/RR; Increased muscle tone of UL & LL No evidence for effect on mortality or long-term outcome
Phenobarbital (prophylactic)	3 1	RCT Cochrane	110	YES	No difference in mortality or long-term outcome Same; but all studies have methodological weakness

Asphyxia - Management

Only supportive care!

Therapeutic hypothermia

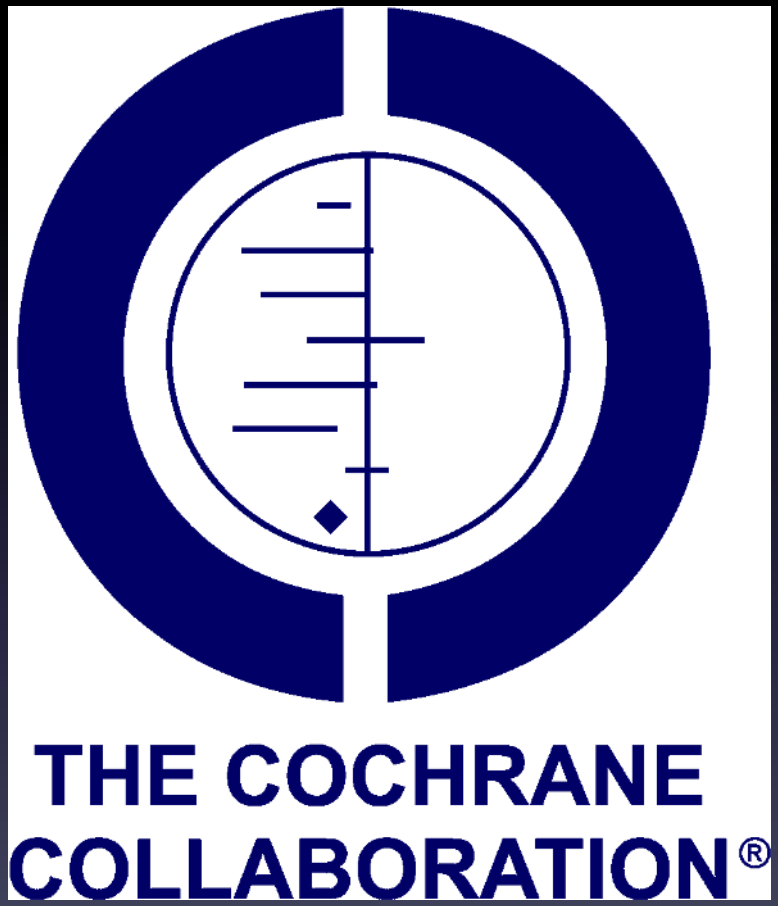



Timing of Pathological Events After Hypoxia-Ischemia
Hypoxia-Ischemia
Asphyxia
Primary
Death
Cytotoxic
Mechanisms
Delayed
Neuronal
Death
Hypothermia
1 hour
6 hours
5 days
Latent Phase

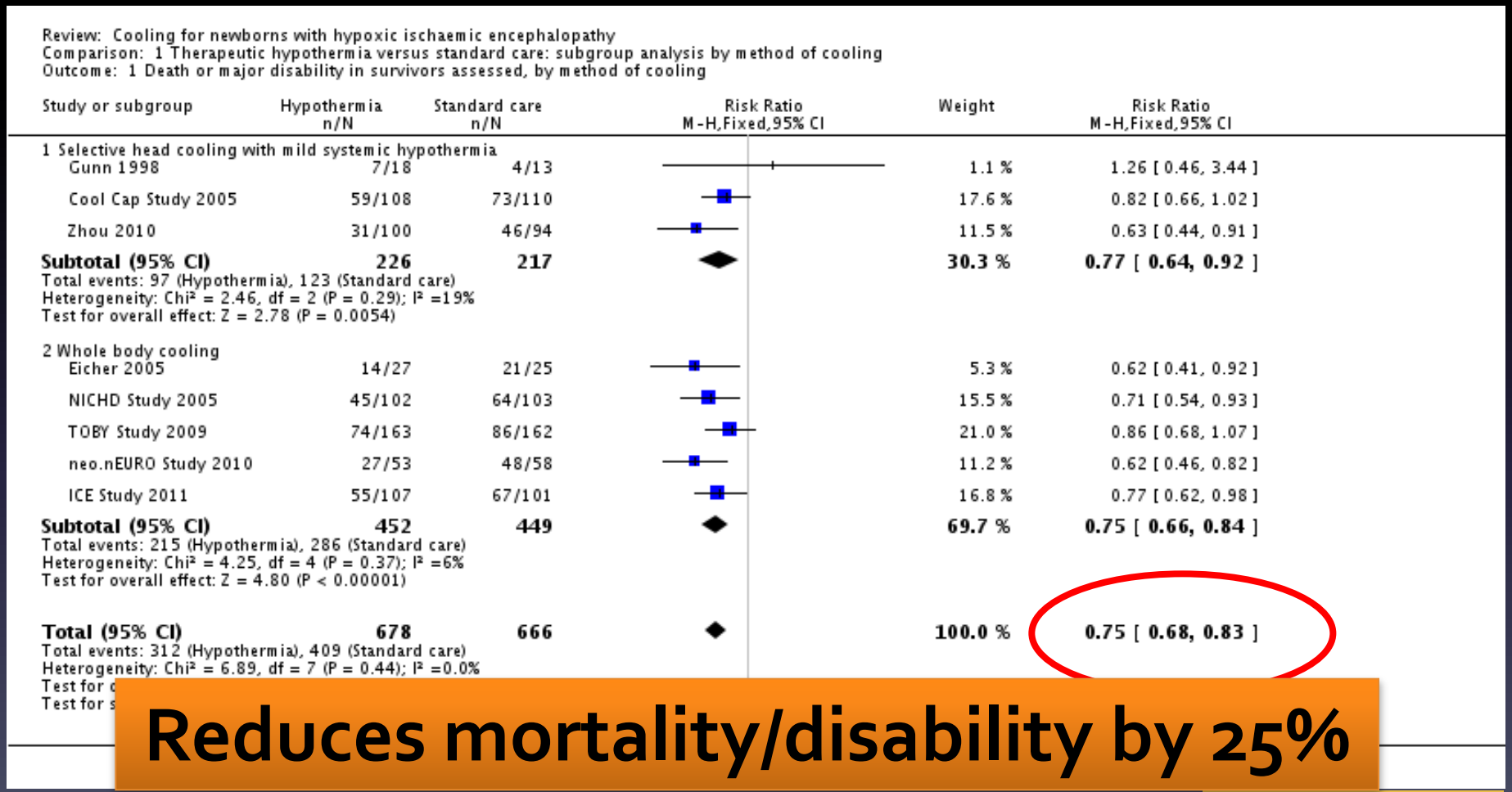
How it acts?

1. ↓ Energy depletion
2. ↓Glutamate release
3. ↑Glutamate reuptake
4. ↓ Free radical generation
5. Blocks downstream mech. of apoptosis/necrosis
6. Inhibits inflammation

Evidence



Is it effective?



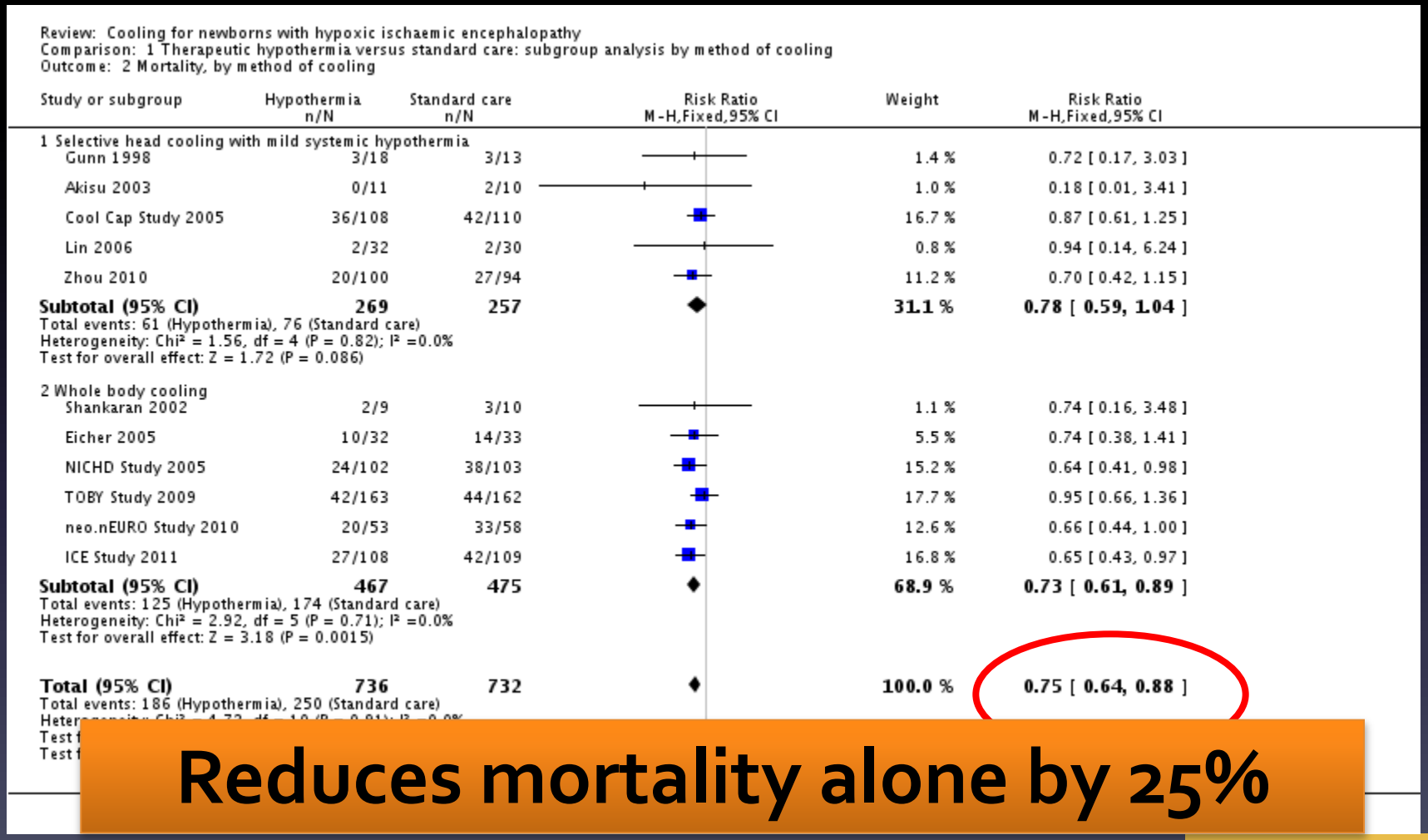
Review: Cooling for newborns with hypoxic ischaemic encephalopathy
Comparison: 1 Therapeutic hypothermia versus standard care: subgroup analysis by method of cooling
Outcome: 1 Death or major disability in survivors assessed, by method of cooling

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Selective head cooling with mild systemic hypothermia					
Gunn 1998	7/18	4/13		1.1 %	1.26 [0.46, 3.44]
Cool Cap Study 2005	59/108	73/110		17.6 %	0.82 [0.66, 1.02]
Zhou 2010	31/100	46/94		11.5 %	0.63 [0.44, 0.91]
Subtotal (95% CI)	**226**	**217**		**30.3 %**	**0.77 [0.64, 0.92]**
Total events: 97 (Hypothermia), 123 (Standard care)					
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					
Eicher 2005	14/27	21/25		5.3 %	0.62 [0.41, 0.92]
NICHD Study 2005	45/102	64/103		15.5 %	0.71 [0.54, 0.93]
TOBY Study 2009	74/163	86/162		21.0 %	0.86 [0.68, 1.07]
neo.nEURO Study 2010	27/53	48/58		11.2 %	0.62 [0.46, 0.82]
ICE Study 2011	55/107	67/101		16.8 %	0.77 [0.62, 0.98]
Subtotal (95% CI)	**452**	**449**		**69.7 %**	**0.75 [0.66, 0.84]**
Total events: 215 (Hypothermia), 286 (Standard care)					
Heterogeneity: Chi² = 4.25, df = 4 (P = 0.37); I² =6%					
Test for overall effect: Z = 4.80 (P < 0.00001)					
Total (95% CI)	**678**	**666**		**100.0 %**	**0.75 [0.68, 0.83]**
Total events: 312 (Hypothermia), 409 (Standard care)					
Heterogeneity: Chi² = 6.89, df = 7 (P = 0.44); I² =0.0%					
Test for					
Test for s					

Reduces mortality/disability by 25%

Cochrane 2013

Is it effective?



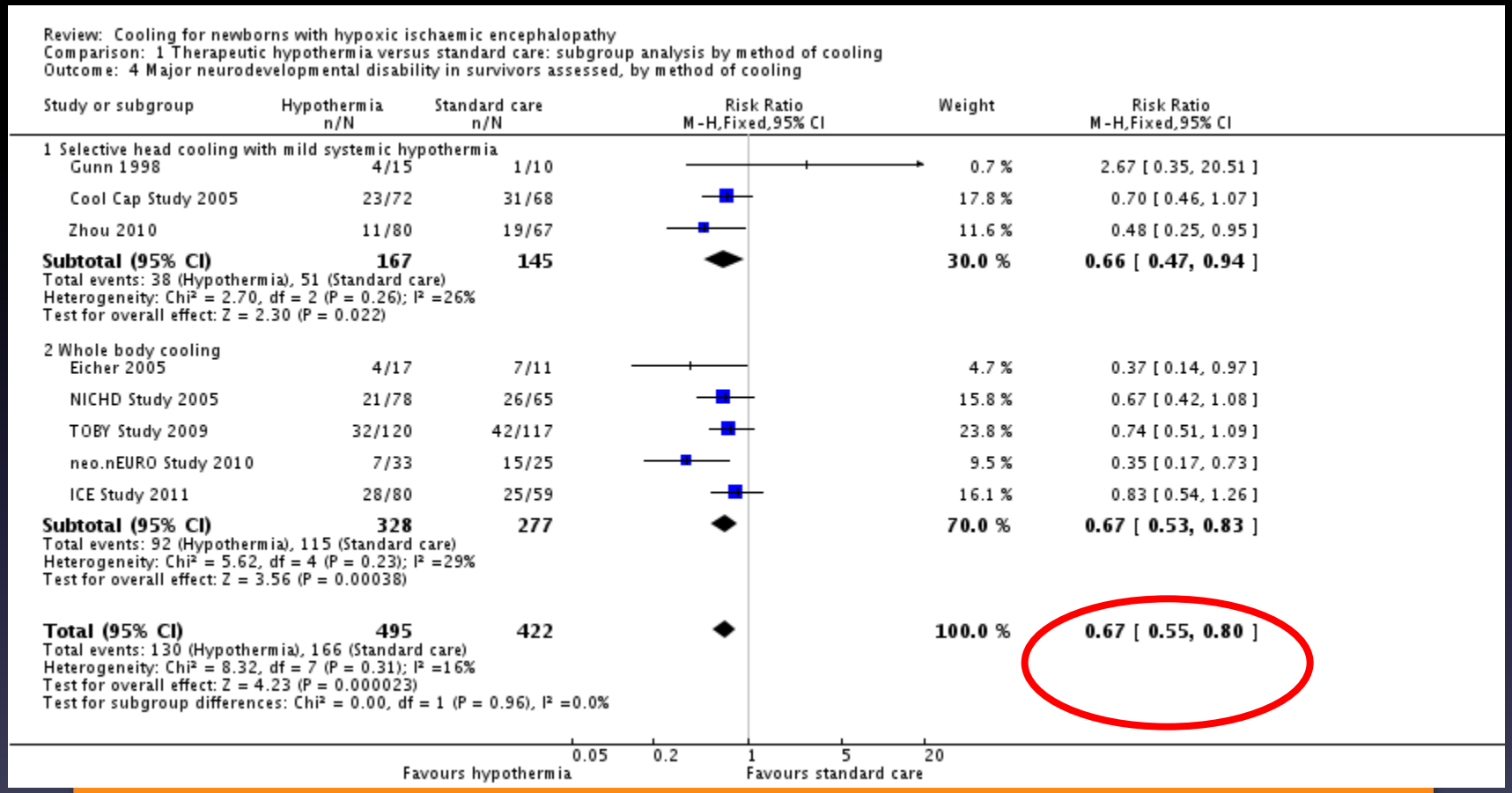
Review: Cooling for newborns with hypoxic ischaemic encephalopathy
Comparison: 1 Therapeutic hypothermia versus standard care: subgroup analysis by method of cooling
Outcome: 2 Mortality, by method of cooling

Study or subgroup	Hypothermia n/N	Standard care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Selective head cooling with mild systemic hypothermia					
Gunn 1998	3/18	3/13		1.4 %	0.72 [0.17, 3.03]
Akisu 2003	0/11	2/10		1.0 %	0.18 [0.01, 3.41]
Cool Cap Study 2005	36/108	42/110		16.7 %	0.87 [0.61, 1.25]
Lin 2006	2/32	2/30		0.8 %	0.94 [0.14, 6.24]
Zhou 2010	20/100	27/94		11.2 %	0.70 [0.42, 1.15]
Subtotal (95% CI)	**269**	**257**		**31.1 %**	**0.78 [0.59, 1.04]**
Total events: 61 (Hypothermia), 76 (Standard care)					
Heterogeneity: Chi² = 1.56, df = 4 (P = 0.82); I² =0.0%					
Test for overall effect: Z = 1.72 (P = 0.086)					
2 Whole body cooling					
Shankaran 2002	2/9	3/10		1.1 %	0.74 [0.16, 3.48]
Eicher 2005	10/32	14/33		5.5 %	0.74 [0.38, 1.41]
NICHD Study 2005	24/102	38/103		15.2 %	0.64 [0.41, 0.98]
TOBY Study 2009	42/163	44/162		17.7 %	0.95 [0.66, 1.36]
neo.nEURO Study 2010	20/53	33/58		12.6 %	0.66 [0.44, 1.00]
ICE Study 2011	27/108	42/109		16.8 %	0.65 [0.43, 0.97]
Subtotal (95% CI)	**467**	**475**		**68.9 %**	**0.73 [0.61, 0.89]**
Total events: 125 (Hypothermia), 174 (Standard care)					
Heterogeneity: Chi² = 2.92, df = 5 (P = 0.71); I² =0.0%					
Test for overall effect: Z = 3.18 (P = 0.0015)					
Total (95% CI)	**736**	**732**		**100.0 %**	**0.75 [0.64, 0.88]**
Total events: 186 (Hypothermia), 250 (Standard care)					

Reduces mortality alone by 25%

Cochrane 2013

Is it effective?



Reduces disability by 33%

Cochrane 2013

Why?

- Any other modality? - No
- Science - Yes
- Evidence - Yes

Standard of care!

Why not to use?

India: Peculiar situation

- Population differences
- Practical issues
- Cost
- Evidence

Population differences

Brain injury – begins *in utero*

- Maternal malnutrition/anemia
- IUGR
- Poor antenatal care
- Home deliveries – poor perinatal care

? Less beneficial

Wilkinson 2010

Population differences…

Sepsis

- Hypothermia
  - affects neutrophil function
  - Can worsen sepsis and pneumonia
- Difficult to differentiate sepsis and asphyxia

Uganda trial – Increased mortality!

Wilkinson 2010

Population differences…

Late referral and others

- Reach after 6 hours
- Most – multiorgan dysfunction
  - Kidneys
  - Heart
- Many – MAS and PPHN

Less effective; may be harmful

Wilkinson 2010

Practical issues

Adverse events

TABLE III SERIOUS ADVERSE EVENTS DURING COOLING

Adverse events	No. (%)
Cardiac arrhythmias	Nil
Hypoglycemia (blood sugar <45 mg/dL)	2 (10%)
Hyperglycemia requiring insulin	3 (15%)
Thrombocytopenia(<100 $\times 10^3/\mu L$)	5 (25%)
Bleeding	1 (5%)
Aposteatonecrosis	3 (15%)
Hypoxemia	1 (5%)
Oliguria (urine output <0.5 mL/kg/h)	1 (5%)

Needs 24-hr monitoring!

Thomas 2011

Cost

Cost – 5 to 30 lakhs!

Evidence in LMIC

OPEN ACCESS Freely available online

PLOS | ONE

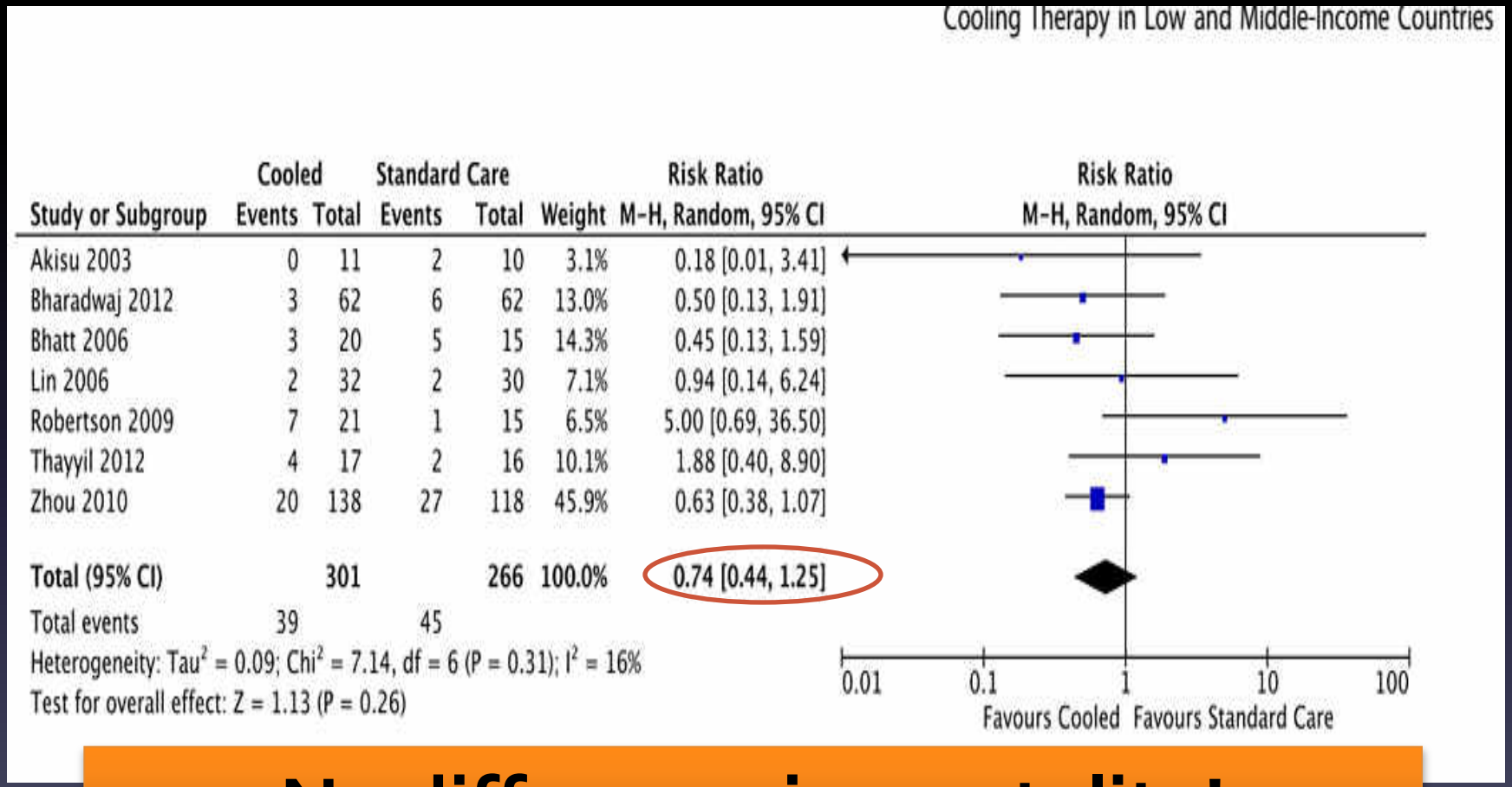
Therapeutic Hypothermia for Neonatal Encephalopathy in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis

Shreela S. Pauliah[1], Seetha Shankaran[2], Angie Wade[3], Ernest B. Cady[4], Sudhin Thayyil[1]*

Evidence in LMIC

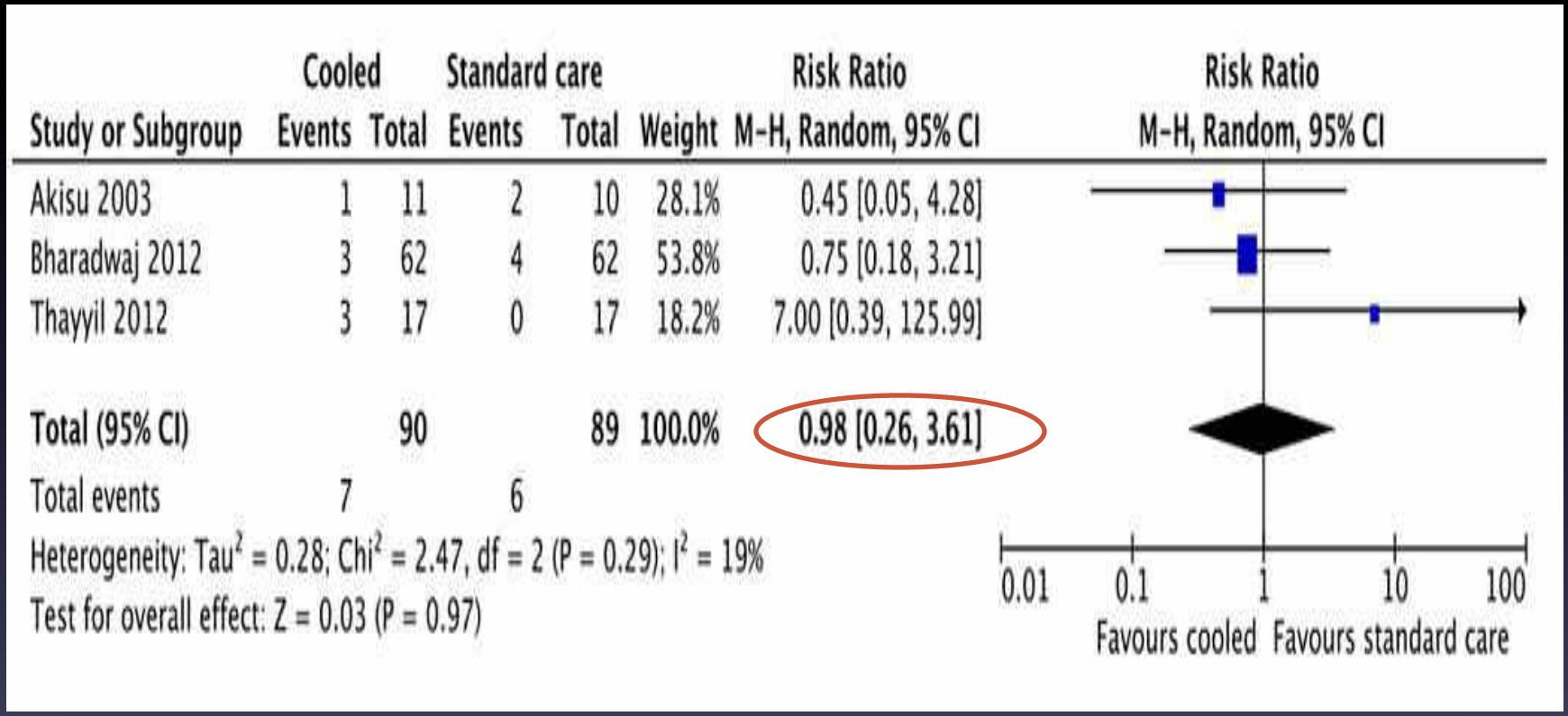
Akisu[20]	Lin[21]	Zhou[22]	Robertson[13]	Thayyil[14]	Bharadwaj[15]	Bhat[18]
Inclusion criteria						
5 min Apgar <6 AND Cord pH<7.1 or base deficit >10 mmol/L AND encephalopathy	5 min Apgar <6 AND Cord pH<7.1 or base deficit >15 mmol/L AND encephalopathy	5 min Apgar <6 AND Cord pH<7 or base deficit ≤16 mmol/L AND need for resuscitation at 5 minutes of age	5 min Apgar <6 AND encephalopathy (Thompson score >5)	5 min Apgar <6 AND encephalopathy (Thompson score >5)	10 min Apgar <6 AND arterial pH≤7 or base excess ≥12 meq AND encephalopathy	10 minute Apgar <5 AND Cord pH<7 and or base deficit of >18 meq/L
Exclusion criteria						
Major congenital malformation, metabolic disorder, chromosomal abnormalities, congenital infection, transitory drug depression	Major congenital abnormalities, persistent pulmonary hypertension	Major congenital abnormalities, maternal fever >38°C, infection, rupture of membranes >18 hours or foul smelling liquor, other encephalopathy	Apnoea or cyanosis, absent cardiac output >10 min	Major congenital malformations, Imminent death at time of randomisation	Major congenital abnormalities, no spontaneous respiration by 20 min, out born babies	Not described

Efficacy: Mortality



No difference in mortality!

Safety: Sepsis



Study or Subgroup	Cooled Events	Cooled Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Random, 95% CI
Akisu 2003	1	11	2	10	28.1%	0.45 [0.05, 4.28]
Bharadwaj 2012	3	62	4	62	53.8%	0.75 [0.18, 3.21]
Thayyil 2012	3	17	0	17	18.2%	7.00 [0.39, 125.99]
Total (95% CI)		**90**		**89**	**100.0%**	**0.98 [0.26, 3.61]**
Total events	7		6			

Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 2.47$, df = 2 (P = 0.29); $I^2 = 19\%$

Test for overall effect: Z = 0.03 (P = 0.97)

No difference in sepsis!

No future?

Should we?

Population differences

Brain injury – begins *in utero*

- Maternal malnutrition/anemia
- Poor antenatal care
- Home deliveries
- IUGR

Research idea 1:

Efficacy of hypothermia in IUGR!

Population differences

Sepsis

- Hypothermia
  - affects neutrophil function
  - Can worsen sepsis and pneumonia
- Difficult to differentiate sepsis and asphyxia

Research idea 2:

Safety in asphyxia *and* sepsis!

Population differences

Late referral and others

- Reach after 6 hours
- Most – multiorgan dysfunction
  - Kidneys
  - Heart
- Many – MAS and PPHN

Early referral!

Practical issues

Level of intensive care

TABLE III SERIOUS ADVERSE EVENTS DURING COOLING

Adverse events	No. (%)
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Bleeding	1 (5%)
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Hypoxemia	1 (5%)
Oliguria (urine output <0.5 mL/kg/h)	1 (5%)

Ensure monitoring, lab facilities, blood bank!

Thomas 2011

Cost

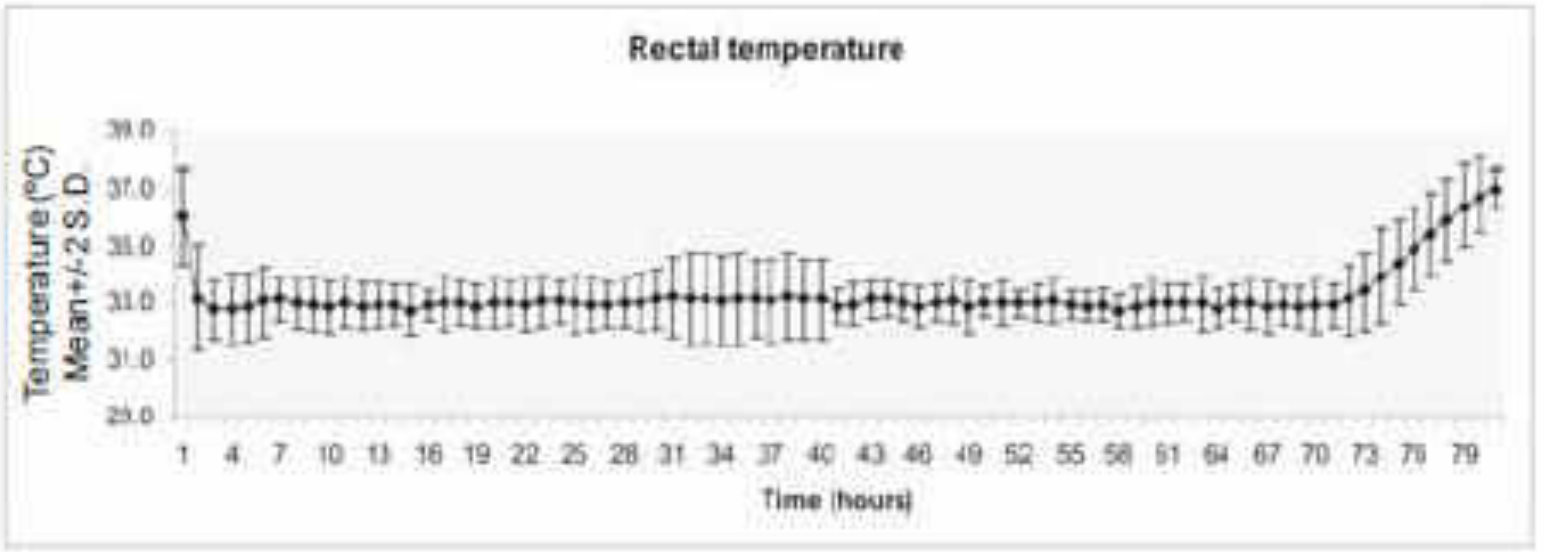
Low-cost devices!

Options

Low tech devices

- Water bottles
- Fans
- Gels
- Ice packs
- Phase changing mattresses

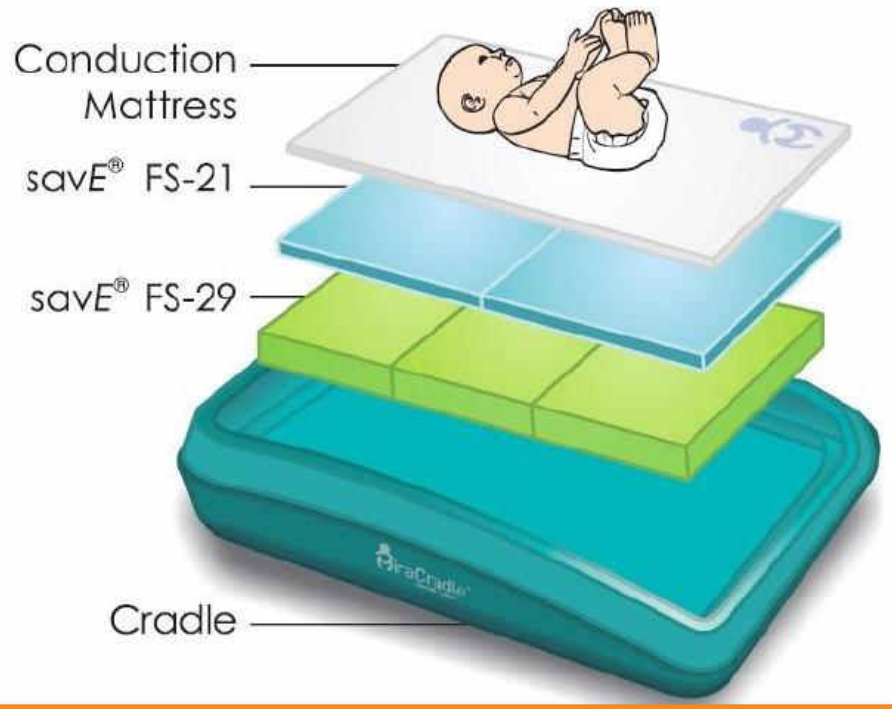
Cooling using ice packs



(*a*) Rectal temperature

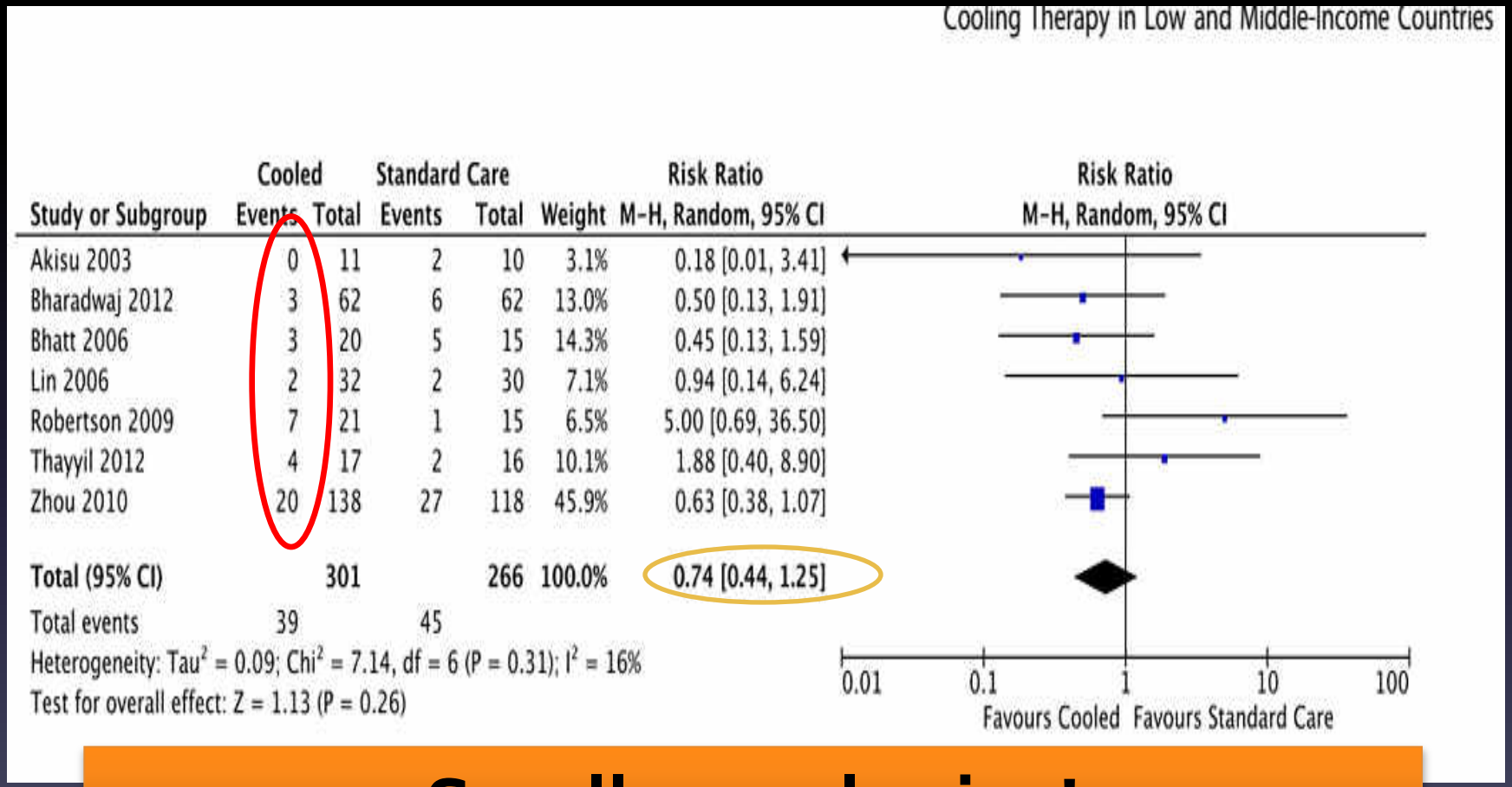
Thomas 2011

Options



Cost: 125 000 INR!

Evidence in LMIC



Small sample size!

2015 ILCOR guidelines

Part 13: Neonatal Resuscitation

2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Myra H. Wyckoff, Chair; Khalid Aziz; Marilyn B. Escobedo; Vishal S. Kapadia; John Kattwinkel; Jeffrey M. Perlman; Wendy M. Simon; Gary M. Weiner; Jeanette G. Zaichkin

Resource-Limited Areas NRP 734

Evidence suggests that use of therapeutic hypothermia in resource-limited settings (ie, lack of qualified staff, inadequate equipment, etc) may be considered and offered under clearly defined protocols similar to those used in published clinical trials and in facilities with the capabilities for multi-

ILCOR recommends!

How?

4P for optimum TH

Place	Personnel	Paraphernalia	Protocols
• **Level-3** NICU (desirable) • Well **established Level-2** NICU	• Trained Pediatrician • **Nursing** staff	• Radiant Warmer • **Cooling device** • **Rectal probes** for temperature monitoring • Multiparametric **monitors** • **ABG machine** • Mechanical ventilator • Glucometer • aEEG (desirable) • MRI (desirable)	• **Timely** identification of HIE • Ensuring TH within 6 h of birth • **Evidence-based standard protocol** for providing and **monitoring TH** • 24 x 7 monitoring • Standardized neurodevelopment follow-up • Continuing staff education

Bhat VB, IJP 2014

Conclusion

- **Level-3 units**
  - **Start cooling** with adequate monitoring
- **Level-2 units**
  - **Establish** facilities required (monitoring; lab)
  - Low-cost devices (if monitoring feasible)
  - Early referral (if no facilities)

Conclusion

Therapeutic hypothermia – Make ourselves ready!