Neonatal Encephalopathy

‘Innovations in diagnosis and management’

Ömer ERDEVE, Professor

Ankara University School of Medicine Children’s Hospital

5th Iranian-Turkish Pediatric Meeting, Antalya (Turkey), 15th November, 2018.

Ankara University
SCHOOL OF MEDICINE
The First Medical School In The Republic of Turkey (1945)

Perinatal asphyxia ….. A nightmare
4 million asphyxia, 1 million death, 1 million severe neurological impairment

Matern Child Health J (2013) 17:1215–1221
DOI 10.1007/s10995-012-1115-7

Rapid Decrease of Neonatal Mortality in Turkey

Gamze Demirel · Basak Tezel · Sema Ozbas · Serife Suna Oguz · Omer Erdeve · Nurdan Uras · Ugur Dilmen

- ✓ It occurs in approximately 2/1000 live births and is associated with a high risk of death or lifelong disability in contrast to the improved perinatal care
- ✓ 5th common cause of below 5 years mortality in the world, and 4th leading neonatal mortality in Turkey!

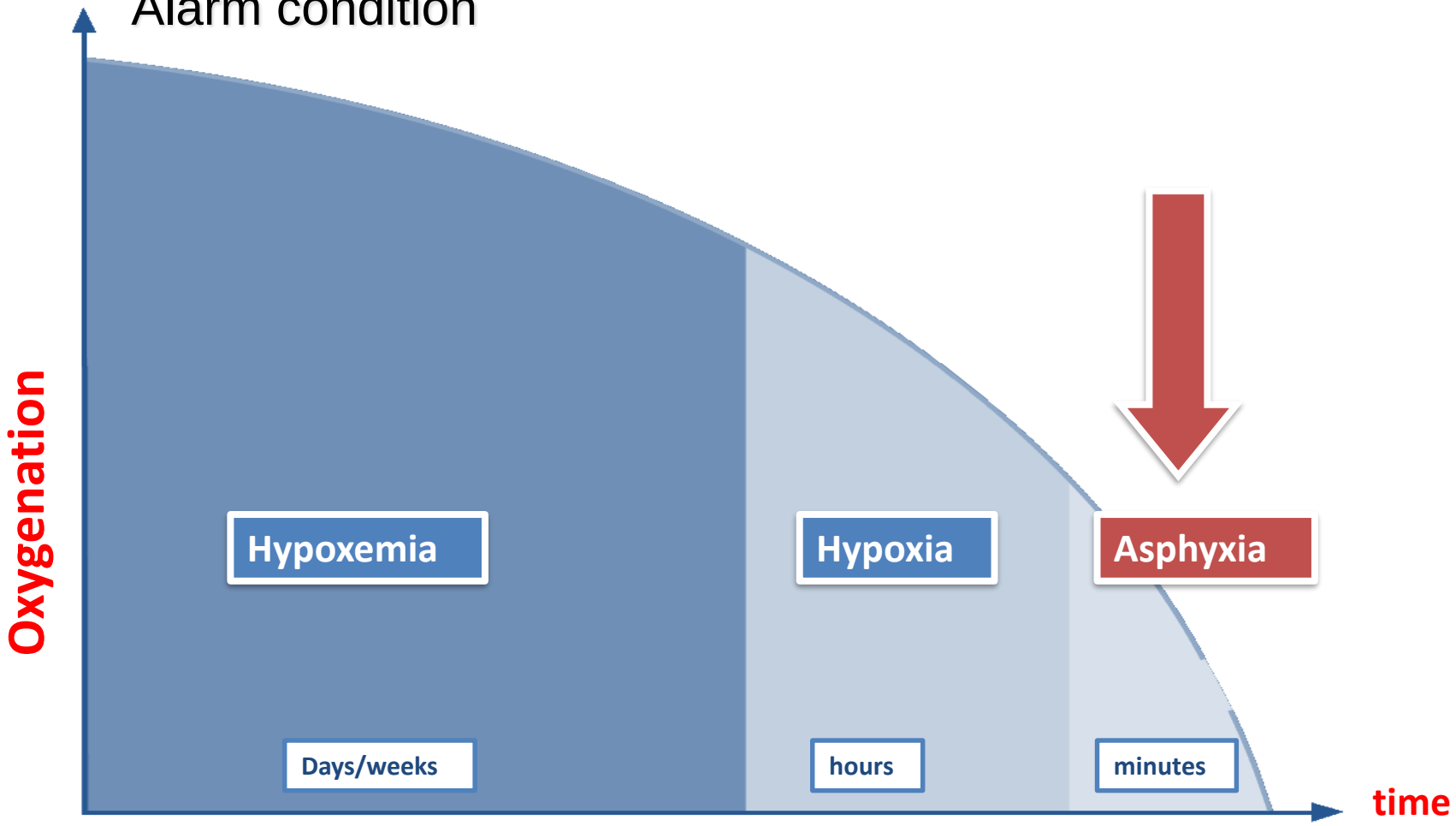
Challenges/questions

- ✓ Terminologic problems - Are all neonatal encephalopathies related to HIE?
- ✓ Is diagnosis easy as defined, or more complicated then we think? New approaches?
- ✓ Why therapeutic hypothermia is effective only in half of the patients?
- ✓ What about treatment modality differences in western and resource-limited settings?
- ✓ Are there any other possible treatment options? State-of-the art!

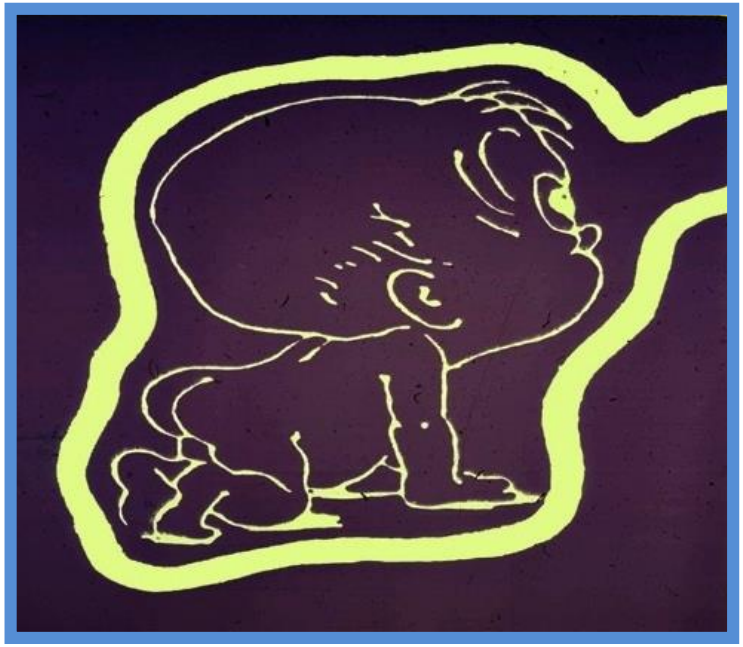
Terminological passages and fetal response

Anaerobic metabolism due to energy and oxygen lack

Alarm condition



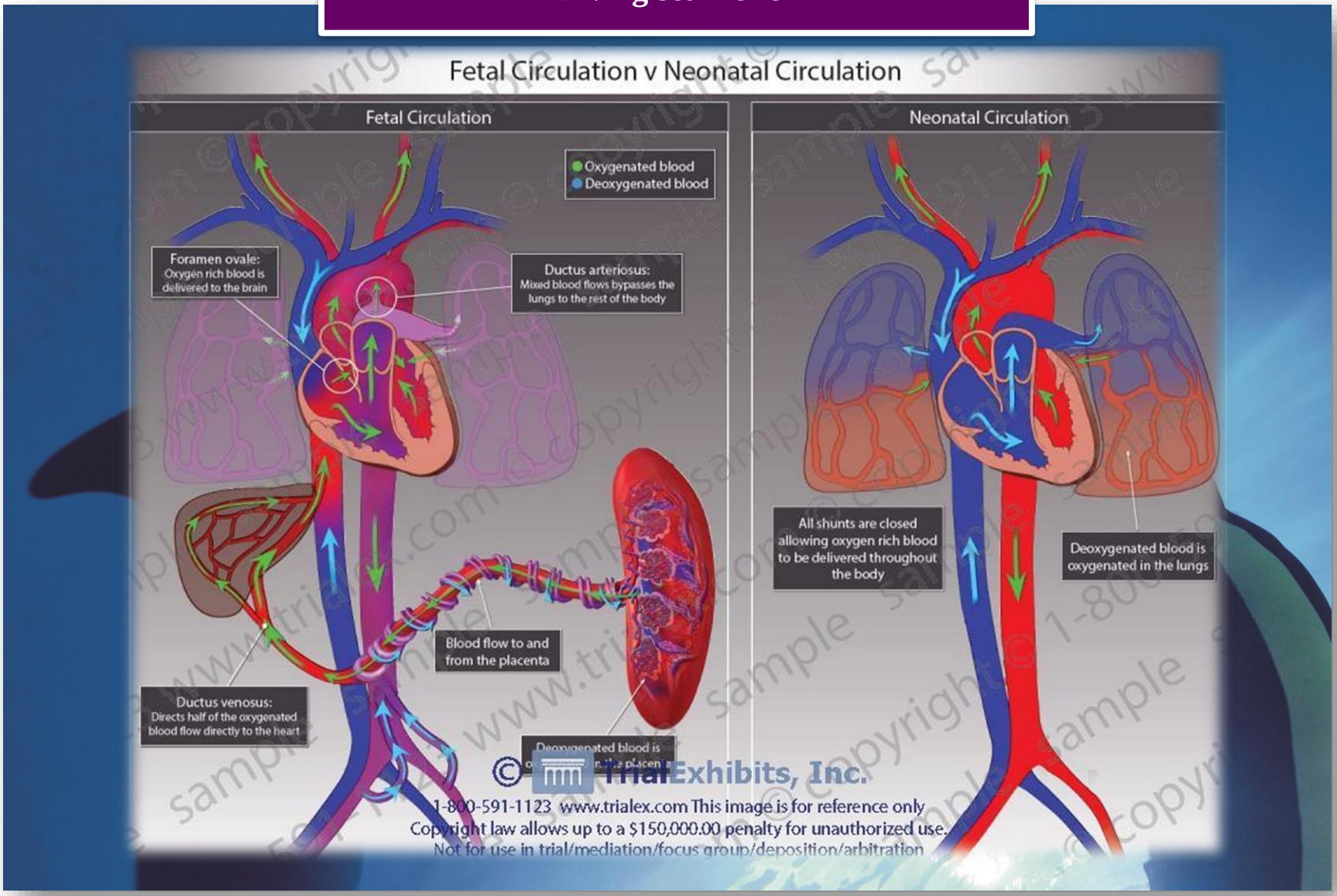
IMPORTANCE OF PREGNANCY FOLLOW-UP and DELIVERY ROOM MANAGEMENT



Emergency; what should I do?

Diving seal reflex

Diving seal reflex



Circulatory response in asphyxia

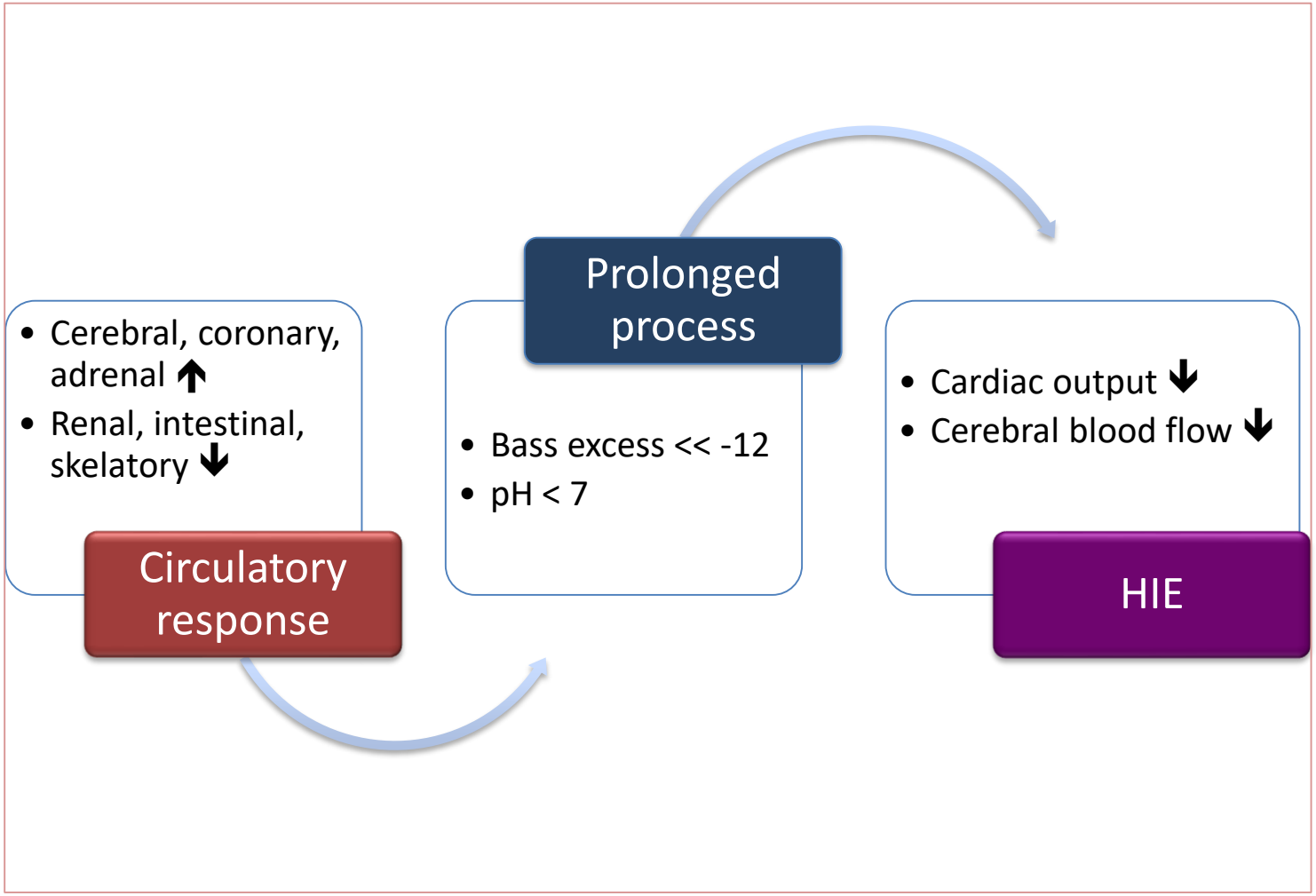
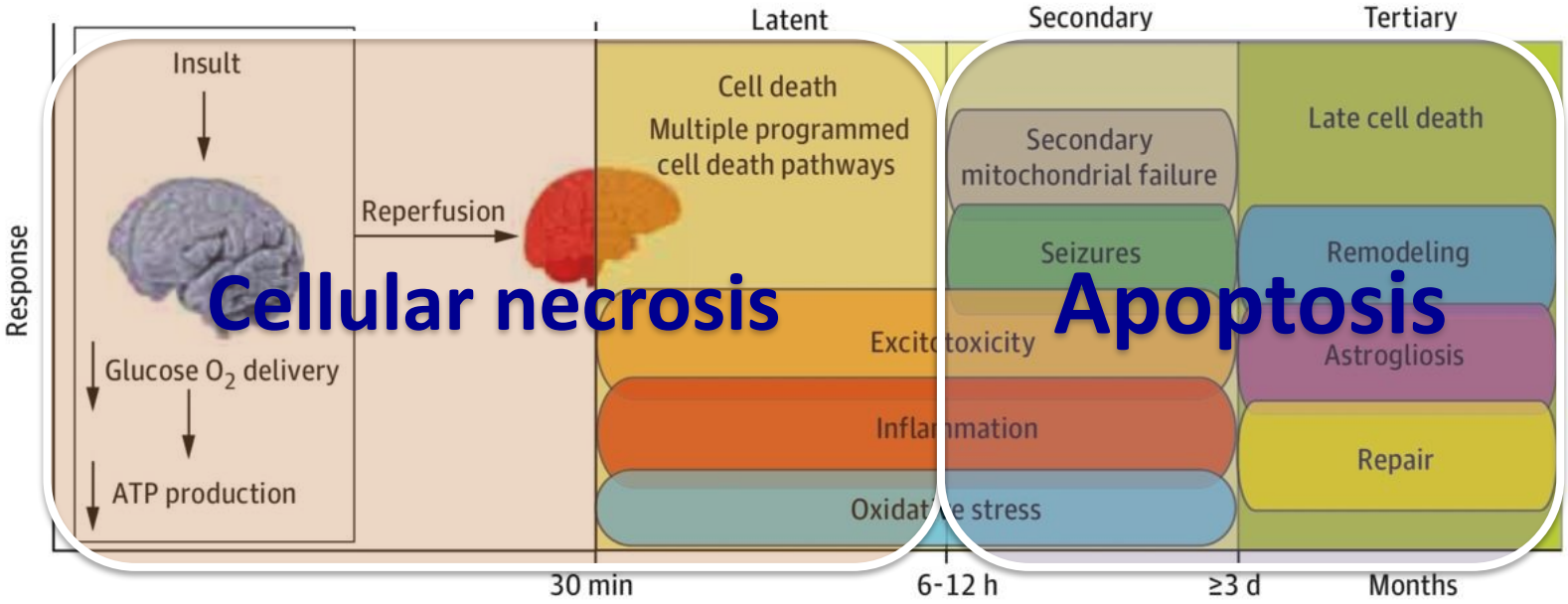


Figure 1. Schematic Overview of the Pathophysiological Features of Hypoxic-Ischemic Encephalopathy



1. **Phase (Fetal hypoxic phase = Energy depletion phase):**
   - Excitatory neurotransmitters, Ca, Hypoxantine
2. **Phase (Ischemia- reperfusion phase):**
   - Free O_2 radicals, inflammation
3. **Phase (Late damage phase):**
   - Apoptosis and down-regulation of neurotropic growth factors

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Does aetiology of neonatal encephalopathy and hypoxic–ischaemic encephalopathy influence the outcome of treatment?

SARAH MCINTYRE[1] | NADIA BADAWI[1,2] | EVE BLAIR[3] | KARIN B NELSON[4,5]

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ABBREVIATION
HIE Hypoxic–ischaemic encephalopathy

2015

Neonatal encephalopathy, a clinical syndrome affecting term-born and late preterm newborn infants, increases the risk of perinatal death and long-term neurological morbidity, especially cerebral palsy. With the advent of therapeutic hypothermia, a treatment designed for hypoxic or ischaemic injury, associated mortality and morbidity rates have decreased. Unfortunately, only about one in eight neonates (95% confidence interval) who meet eligibility criteria for therapeutic cooling apparently benefit from the treatment. Studies of infants in representative populations indicate that neonatal encephalopathy is a potential result of a variety of antecedents and that asphyxial complications at birth account for only a small percentage of neonatal encephalopathy. In contrast, clinical case series suggest that a large proportion of neonatal encephalopathy is hypoxic or ischaemic, and trials of therapeutic hypothermia are specifically designed to include only infants exposed to hypoxia or ischaemia. This review addresses the differences, definitional and methodological, between infants studied and investigations undertaken, in population studies compared with cooling trials. It raises the question if there may be subgroups of infants with a clinical diagnosis of hypoxic-ischaemic encephalopathy (HIE) in whom the pathobiology of neonatal neurological depression is not fundamentally hypoxic or ischaemic and, therefore, for whom cooling may not be beneficial. In addition, it suggests approaches to future trials of cooling plus adjuvant therapy that may contribute to further improvement of care for these vulnerable neonates.

Neonatal encephalopathy is a clinical syndrome of disordered neurological function occurring in the first days of life in term-born and late preterm neonates and is characterized by difficulty initiating and maintaining respiration, an abnormal level of consciousness, depression of tone and reflex responses, and often seizures. This symptom complex affects about 3 in every 1000 births, and is an important predictor of perinatal death and a major contributor to long-term adverse neurological outcomes, particularly cerebral palsy (CP).[1,2] Evidence from clinical and experimental studies agrees that some instances of neonatal encephalopathy are related to hypoxic-ischaemic injury, but the proportions of neonatal encephalopathy attributed to recent asphyxial events vary with the definitions used and the methodology of the investigations. Studies of infants in representative populations indicate that asphyxial complications at birth account for only a minority of neonatal encephalopathy. These population-based studies also identify other factors that contribute to increased risk of neonatal encephalopathy, such as intrauterine exposure to inflammation or fetal growth restriction, and note that some non-asphyxial factors can produce a clinical picture that closely mimics hypoxia–ischaemia.[3–5]

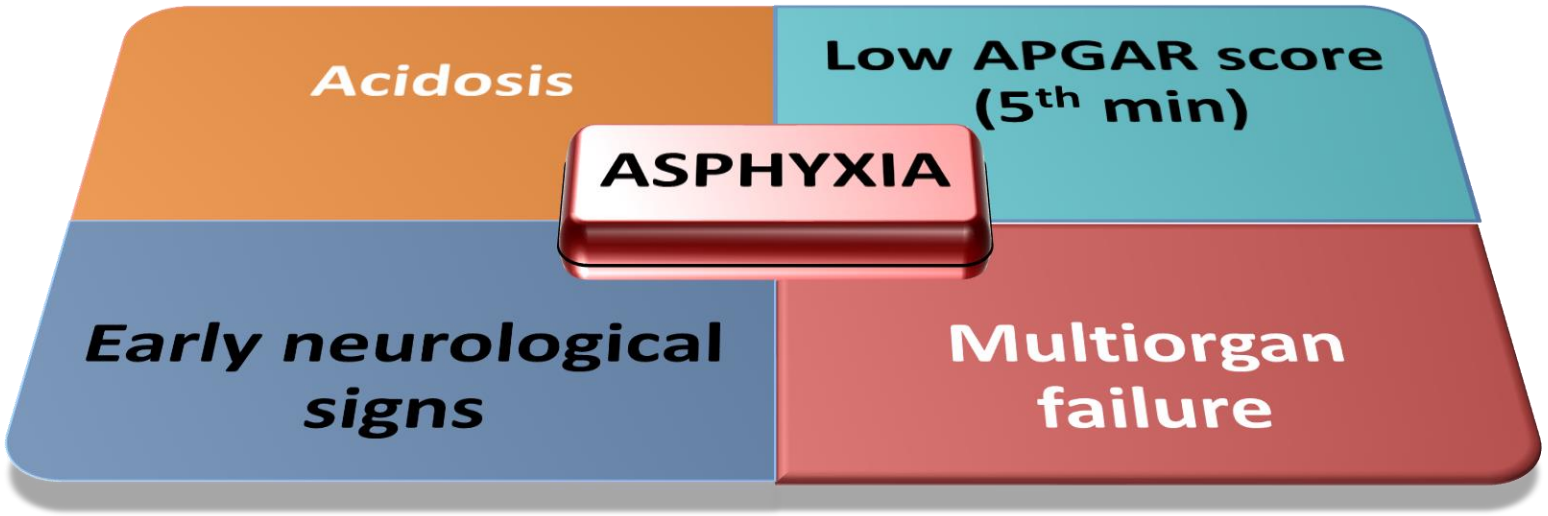
In contrast, studies of neonatal cooling have approached this topic from the point of view of identifying neonates who might benefit from a treatment designed and proven to ameliorate the effects of acute asphyxial injury; they wish to identify and treat infants with hypoxic–ischaemic encephalopathy (HIE). The clinical literature pertaining to therapeutic cooling claims that acute asphyxial insult is the predominant cause of brain injury in neonates who are cooled (as anticipated if selection were appropriate), with little consideration given to the potential role of antenatal factors. However, throughout the cooling literature, the terms neonatal encephalopathy and HIE are used interchangeably, and inconsistencies in terminology are not limited to the cooling literature. In total population studies, HIE is considered a subtype of neonatal encephalopathy. These differences in terminology give rise to some of the differences in opinion with respect to the proportion of infants that develop neonatal encephalopathy as a result of events in the antepartum and intrapartum periods, and, specifically, as a result of intrapartum asphyxial events.

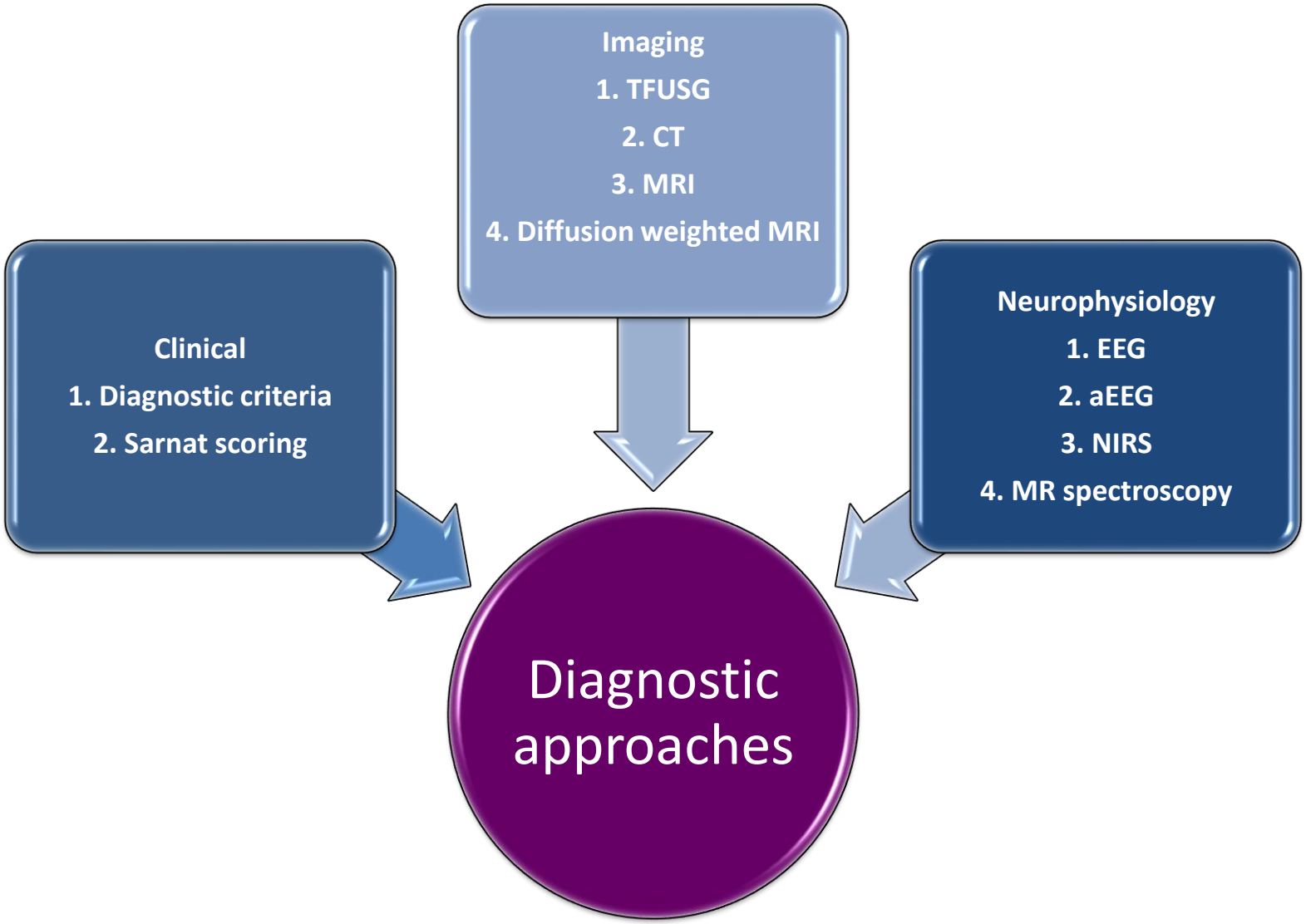
Definitional problems of encephalopathy aside, evidence from 11 randomized clinical trials indicates that therapeutic cooling decreases mortality and long-term neurological

 DOI: 10.1111/dmcn.12725

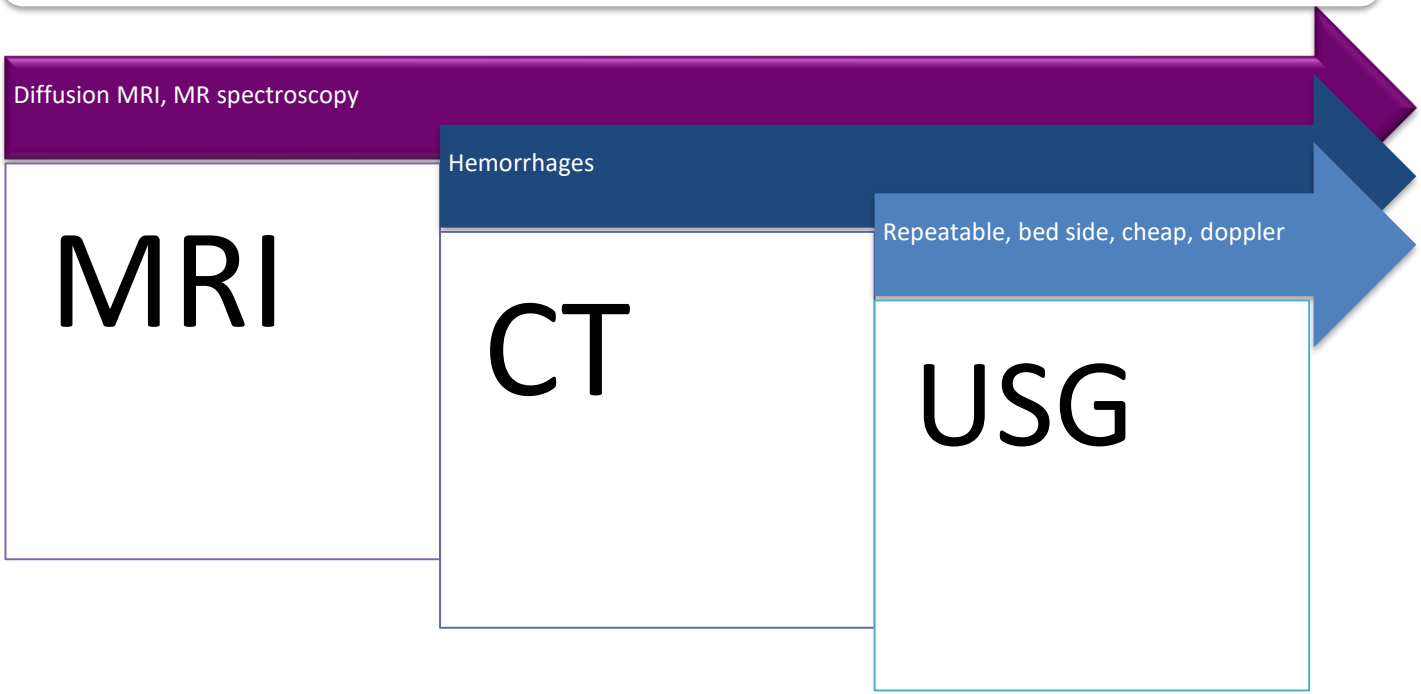
- **Neonatal encephalopathy may be due to many causes**
  - IUGR
  - Maternal diseases
  - Thrombophilia
  - **Fetal inflammation, infections**
  - **“HIE”**
- Differential diagnosis:
  - Detailed perinatal history
  - Placental pathology (Microvillitis)
  - Comprehensive laboratory
  - Genetic and genomic investigations

Prolonged hypoxemia, hypercapnia and disturbed gas exchange leading to acidosis




Imaging
1. TFUSG
2. CT
3. MRI
4. Diffusion weighted MRI
Clinical
1. Diagnostic criteria
2. Sarnat scoring
Neurophysiology
1. EEG
2. aEEG
3. NIRS
4. MR spectroscopy
Diagnostic approaches

Diagnostic neuro-imaging



aEEG

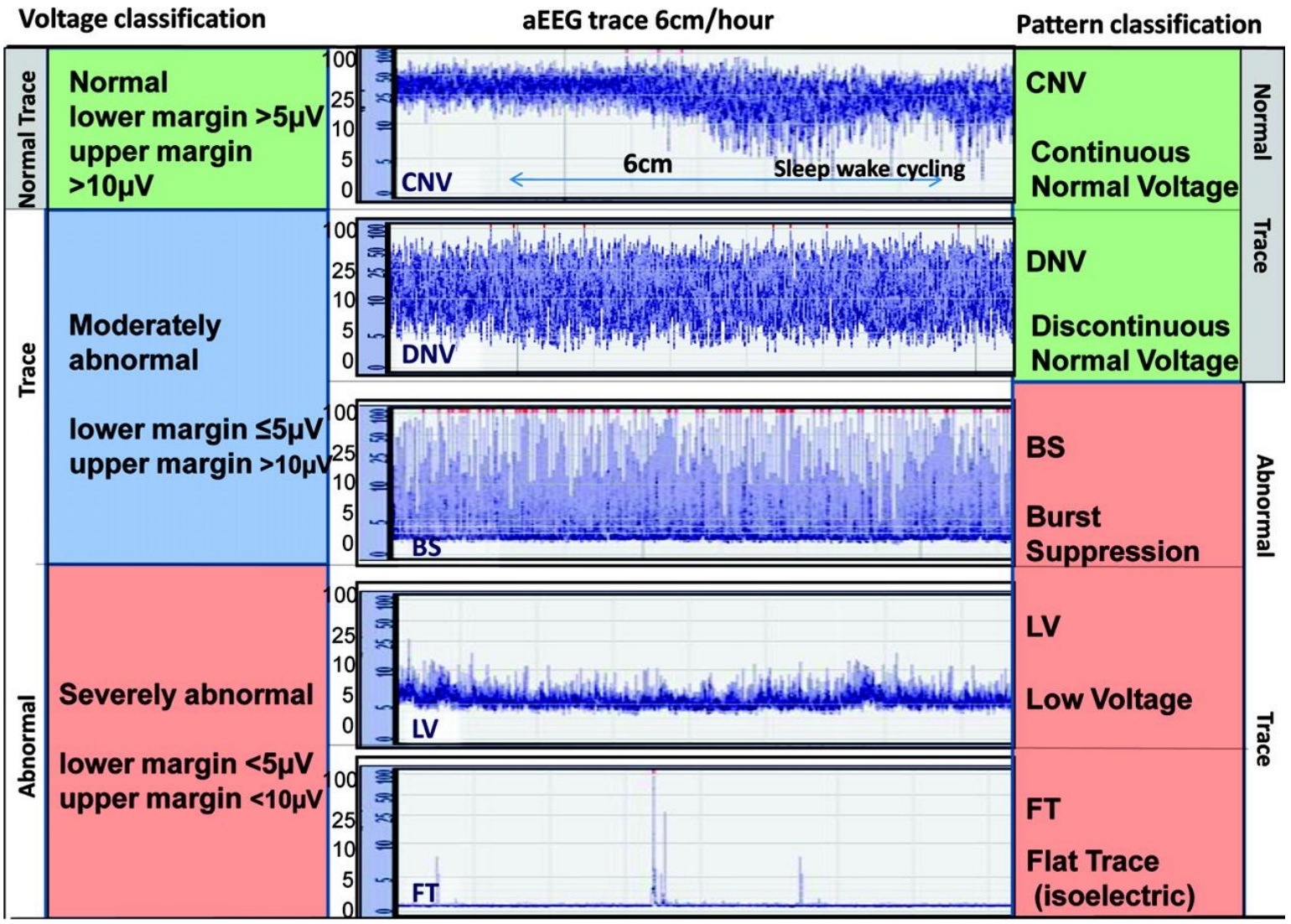
Near infra-red spectroscopy

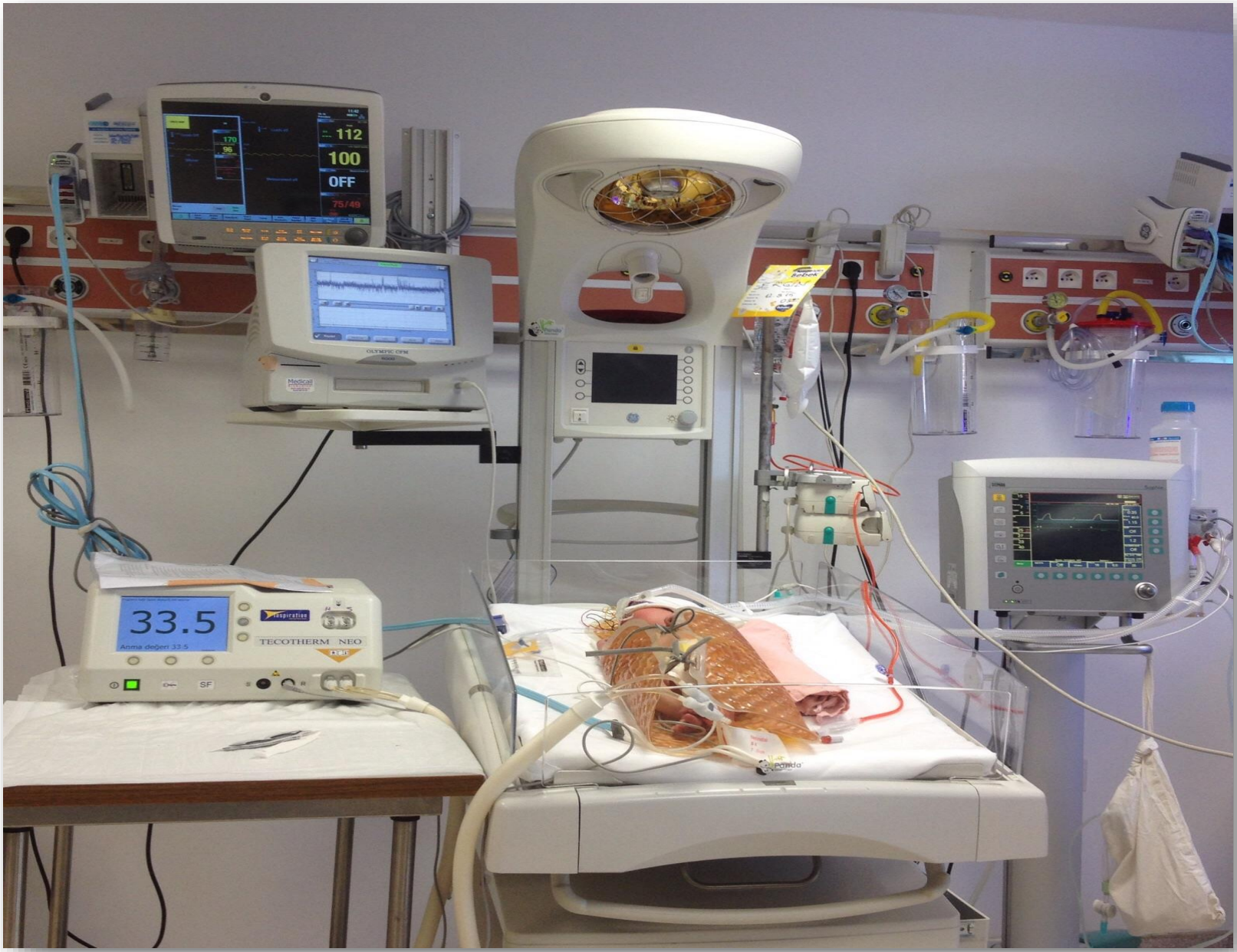
aEEG and NIRS are increasingly used as bedside tools in NICUs to monitor brain function.

Omer Erdeve

Clin Perinatol. 2016 Sep;43(3):511-27.

aEEG


Voltage classification
aEEG trace 6cm/hour
Pattern classification
Normal Trace
Trace
Abnormal
Normal
lower margin >5μV
upper margin
>10μV
Moderately
abnormal
lower margin ≤5μV
upper margin >10μV
Severely abnormal
lower margin <5μV
upper margin <10μV
100
25
10
5
0
CNV
6cm
Sleep wake cycling
DNV
BS
LV
FT
CNV
Continuous
Normal Voltage
DNV
Discontinuous
Normal Voltage
BS
Burst
Suppression
LV
Low Voltage
FT
Flat Trace
(isoelectric)
Normal
Trace
Abnormal
Trace



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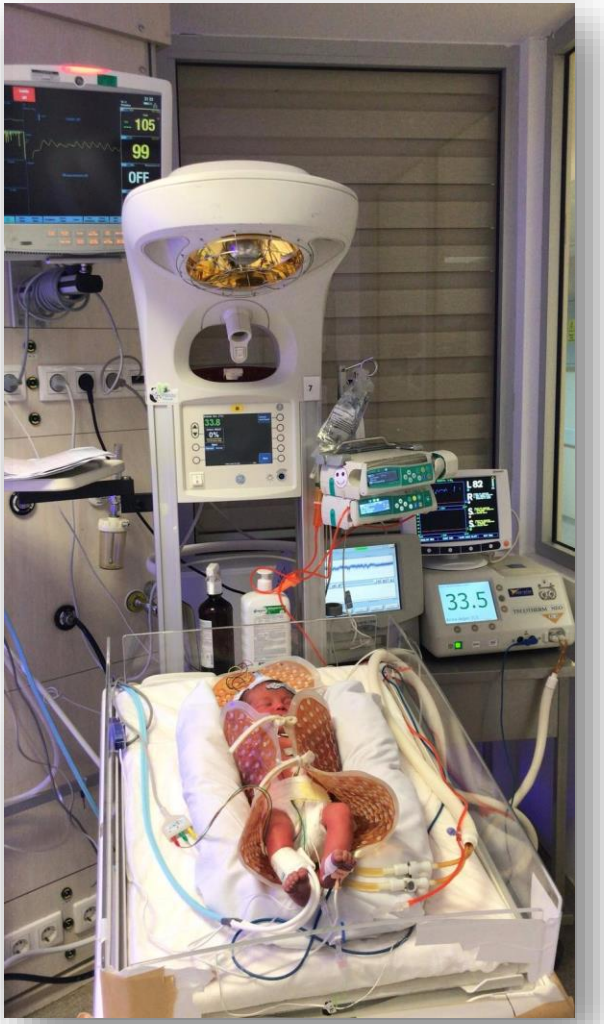
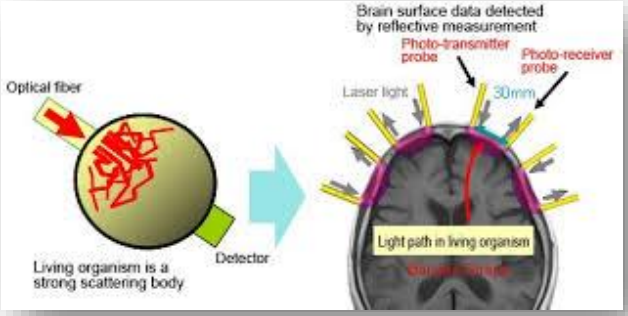
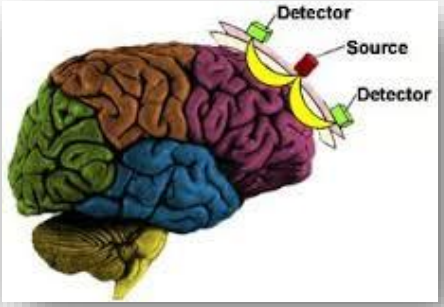
NIRS

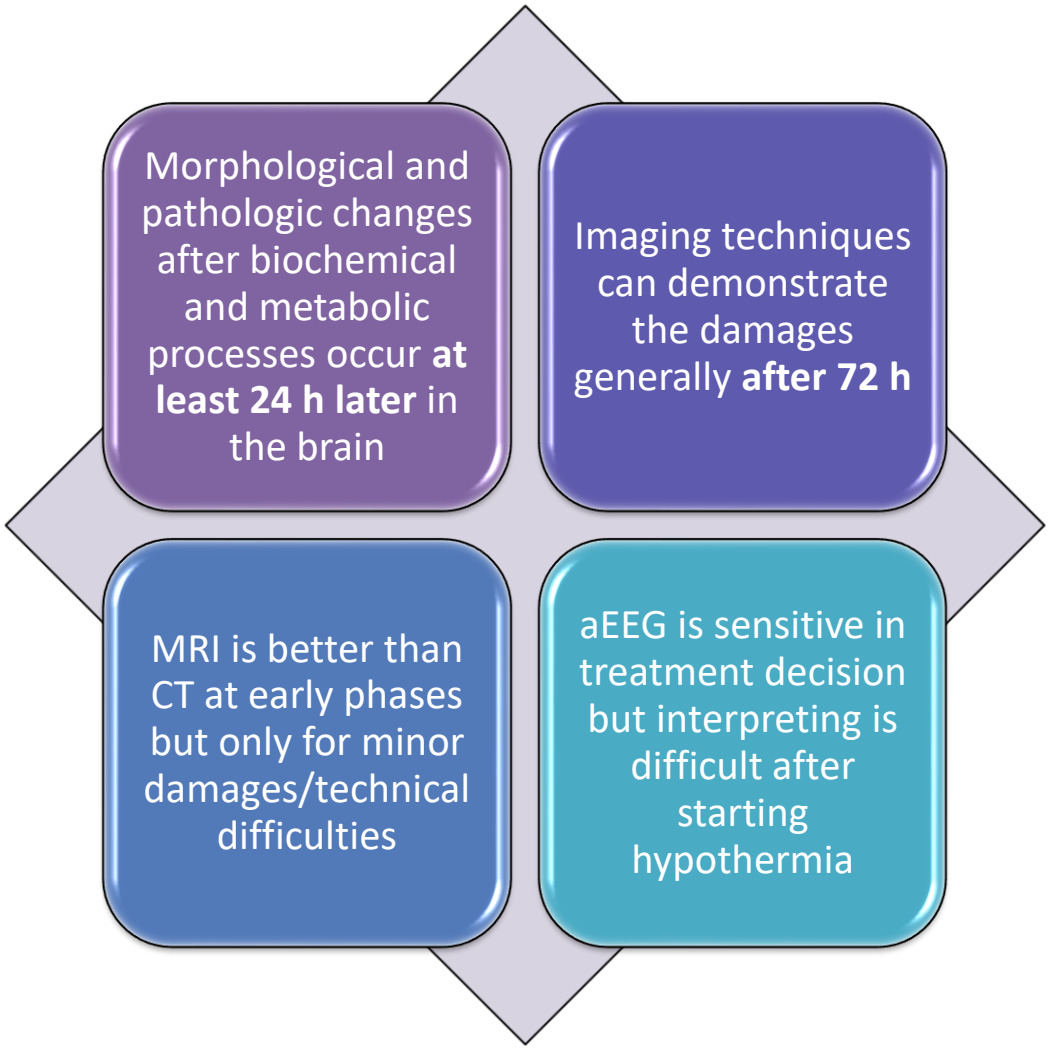




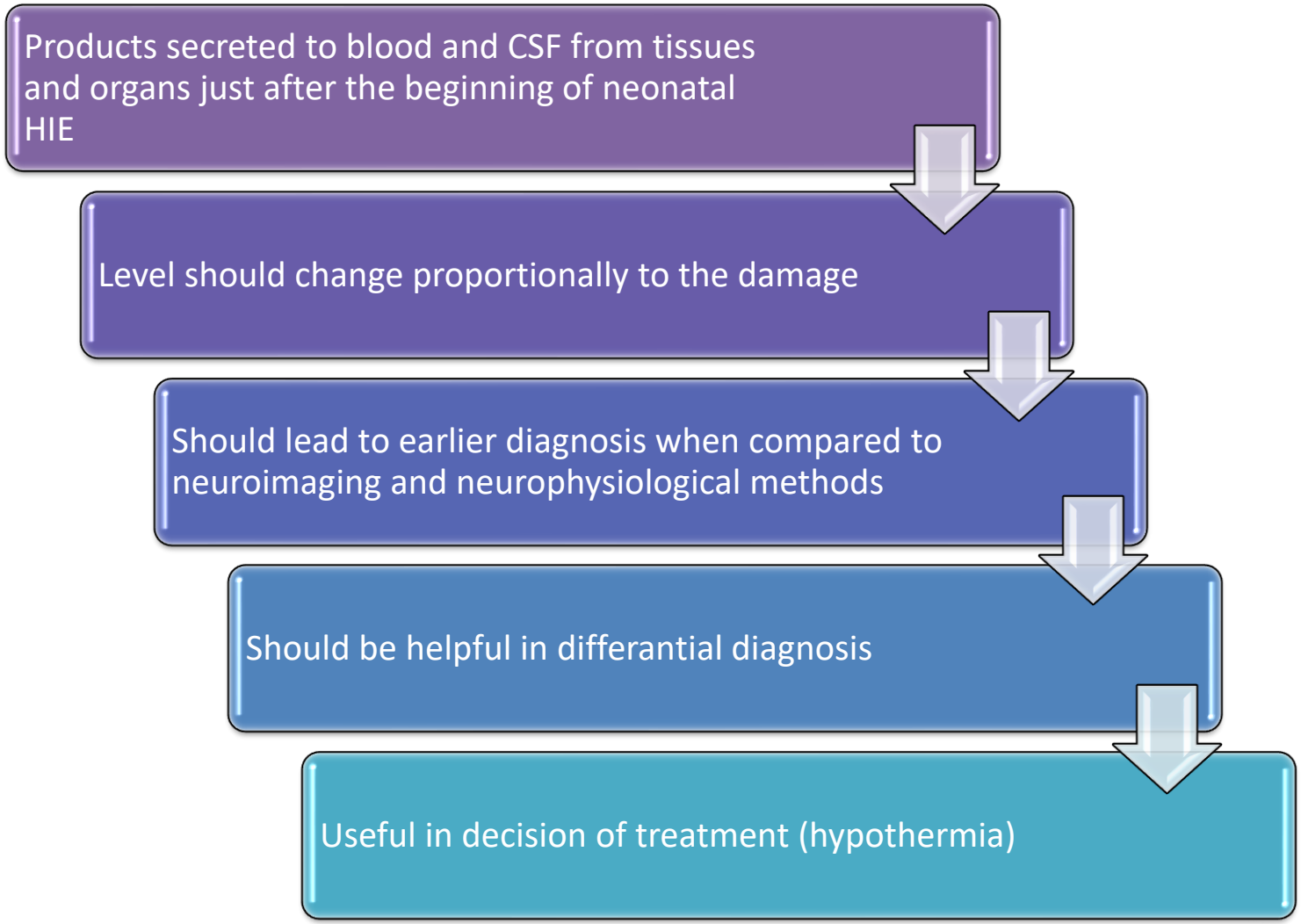


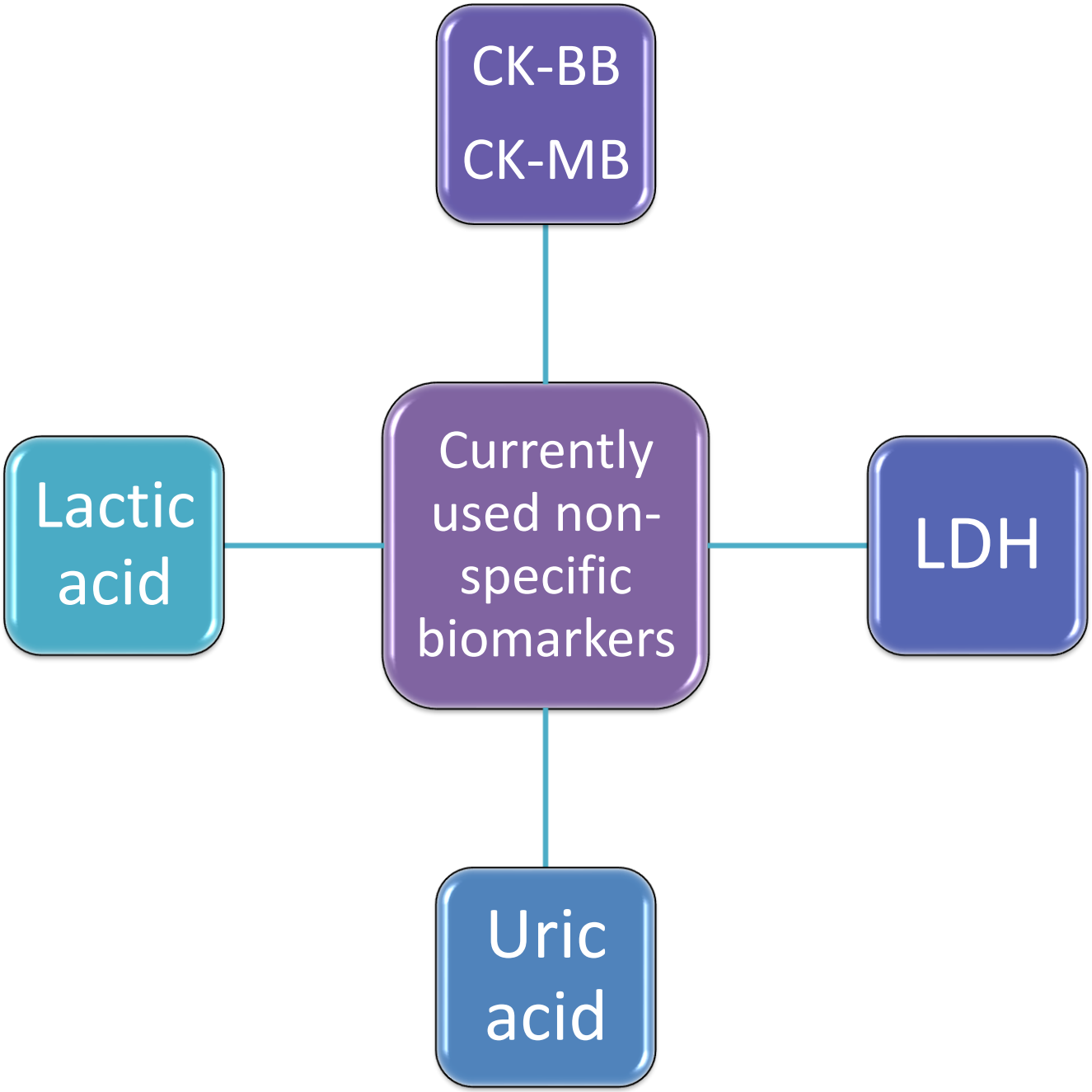
Ömer Erdeve

Limitations in neuroimaging and neurophysiology

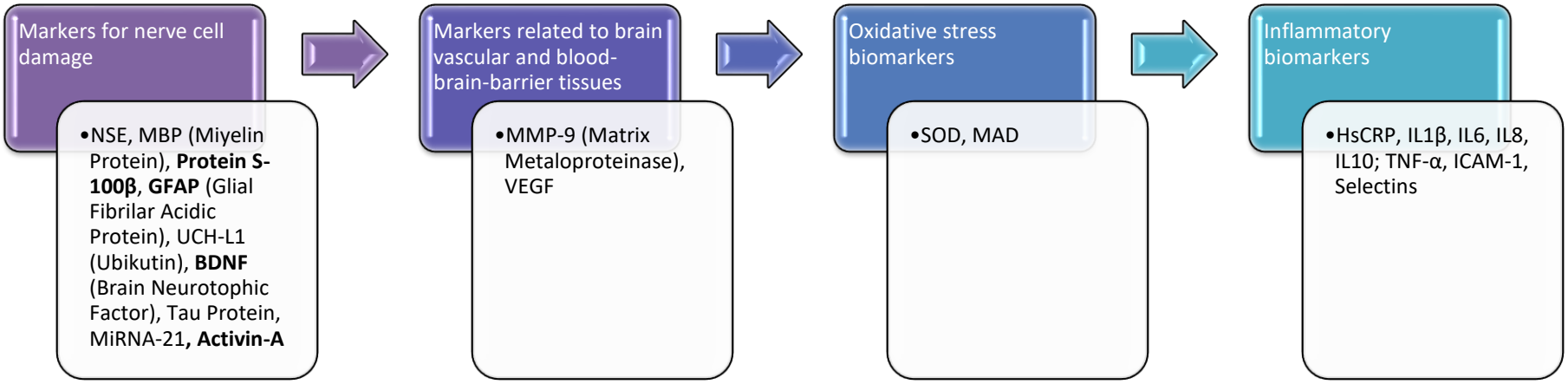


Biomarkers


Products secreted to blood and CSF from tissues and organs just after the beginning of neonatal HIE
Level should change proportionally to the damage
Should lead to earlier diagnosis when compared to neuroimaging and neurophysiological methods
Should be helpful in differantial diagnosis
Useful in decision of treatment (hypothermia)


CK-BB
CK-MB
Lactic acid
Currently used non-specific biomarkers
LDH
Uric acid

Neonatal HIE biomarkers under research



There are no easily available and specific biomarkers for clinical use

Children 2018, 5, 99; doi:10.3390/children5070099
Clin Chemica Acta 2015; 450: 282

Molecules **2015**, *20*, 7000-7016; doi:10.3390/molecules20047000

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Review

Perinatal Asphyxia: A Review from a Metabolomics Perspective

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Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 254076, 9 pages
http://dx.doi.org/10.1155/2015/254076

Review Article

Metabolomic Profiling in Perinatal Asphyxia: A Promising New Field

Niamh M. Denihan, Geraldine B. Boylan, and Deirdre M. Murray

Neonatal Brain Research Group, Department of Paediatrics and Child Health and the Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork and Cork University Maternity Hospital, Wilton, Cork, Ireland

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Received 17 October 2014; Revised 7 January 2015; Accepted 8 January 2015

Far future:
Metabolomics of Krebs Cycle

Delivery room interventions

Maintaining oxygen and energy supplies to vital organs

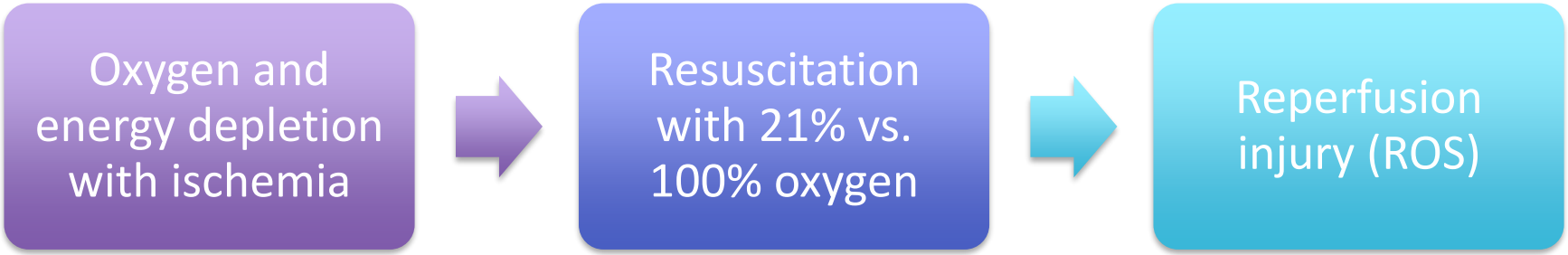
- Respiratory support
- Circulatory support
- Oxygen
- **Avoid hyperthermia (NRP)**
- Avoid hypoglycemia
- Monitorization

Advanced treatments in the NICU

Room air or 100% oxygen for resuscitation of infants with perinatal depression

Vadim S. Ten and Dzmitry Matsiukevich

Current Opinion in Pediatrics 2009, 21:188–193



- Increasing the oxidative damage vs. any delay in oxygenation

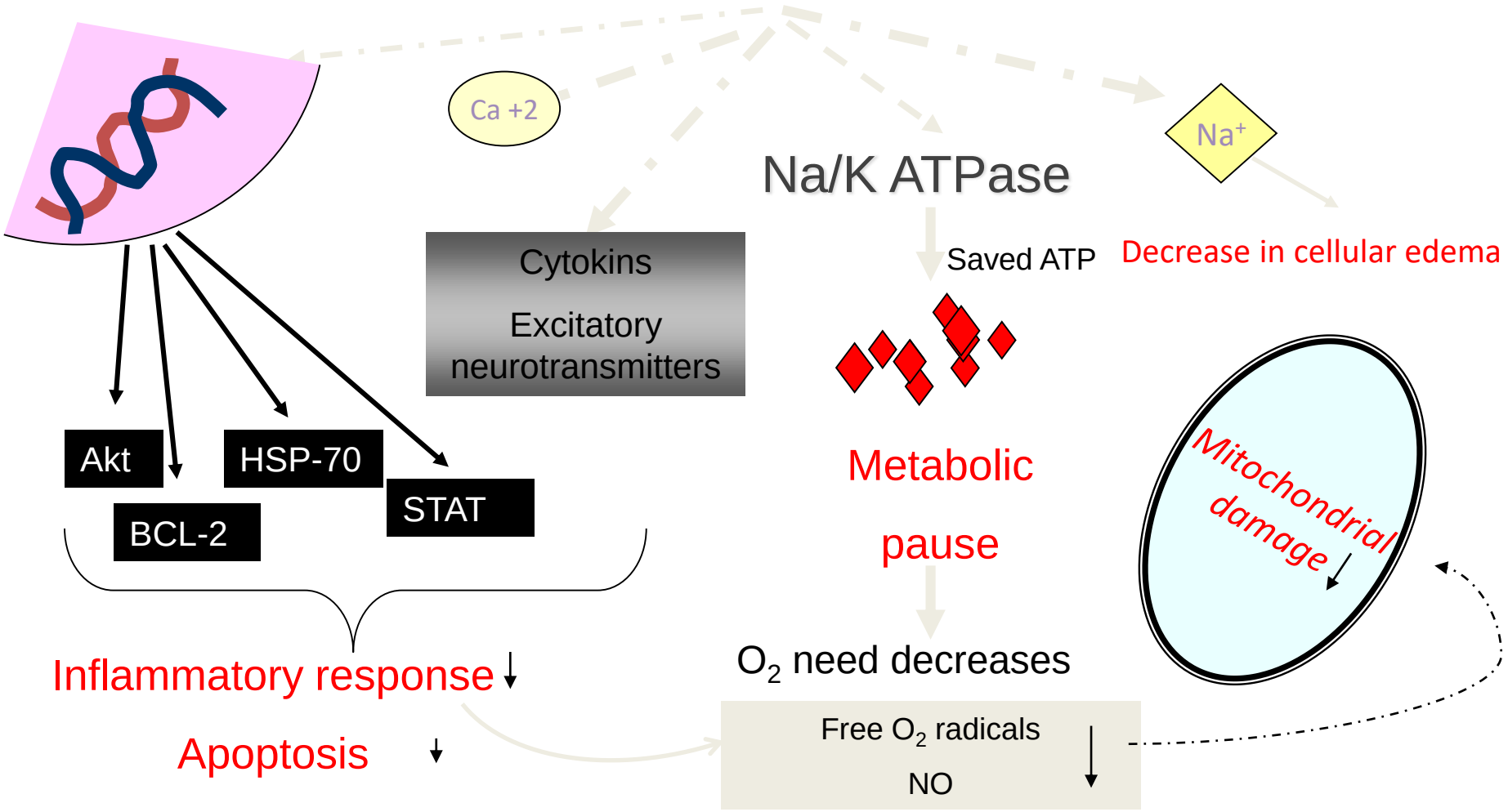
- **Resair 2**: Only 25.7% of patients is changedfroom room-air 100%
- **Vento**: In 75% of patients with 1 min APGAR 1-7 room-air is sufficient

SUGGESTION

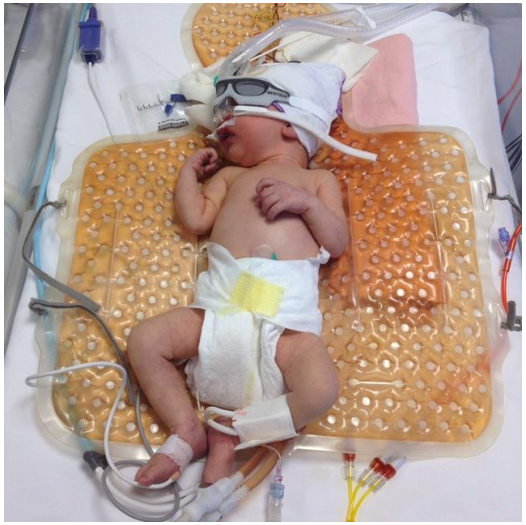
- Patients with adequate circulation (HR>60); room-air
- Arrest or depressed (HR<60) patients; higher oxygen

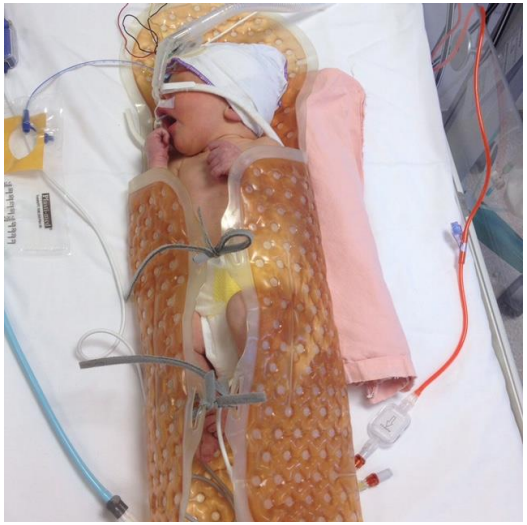
The only targeted treatment for HIE is therapeutic hypothermia

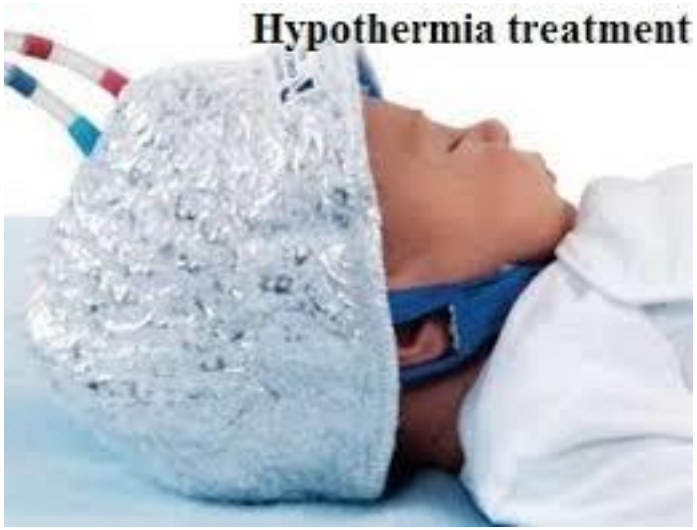
Omer Erdeve


Hypothermia
Ca +2
Na+
Na/K ATPase
Saved ATP
Decrease in cellular edema
Cytokins
Excitatory neurotransmitters
Akt
HSP-70
STAT
BCL-2
Metabolic pause
Mitochondrial damage
Inflammatory response
Apoptosis
O2 need decreases
Free O2 radicals
NO

Whole-body cooling or Cool cap







PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

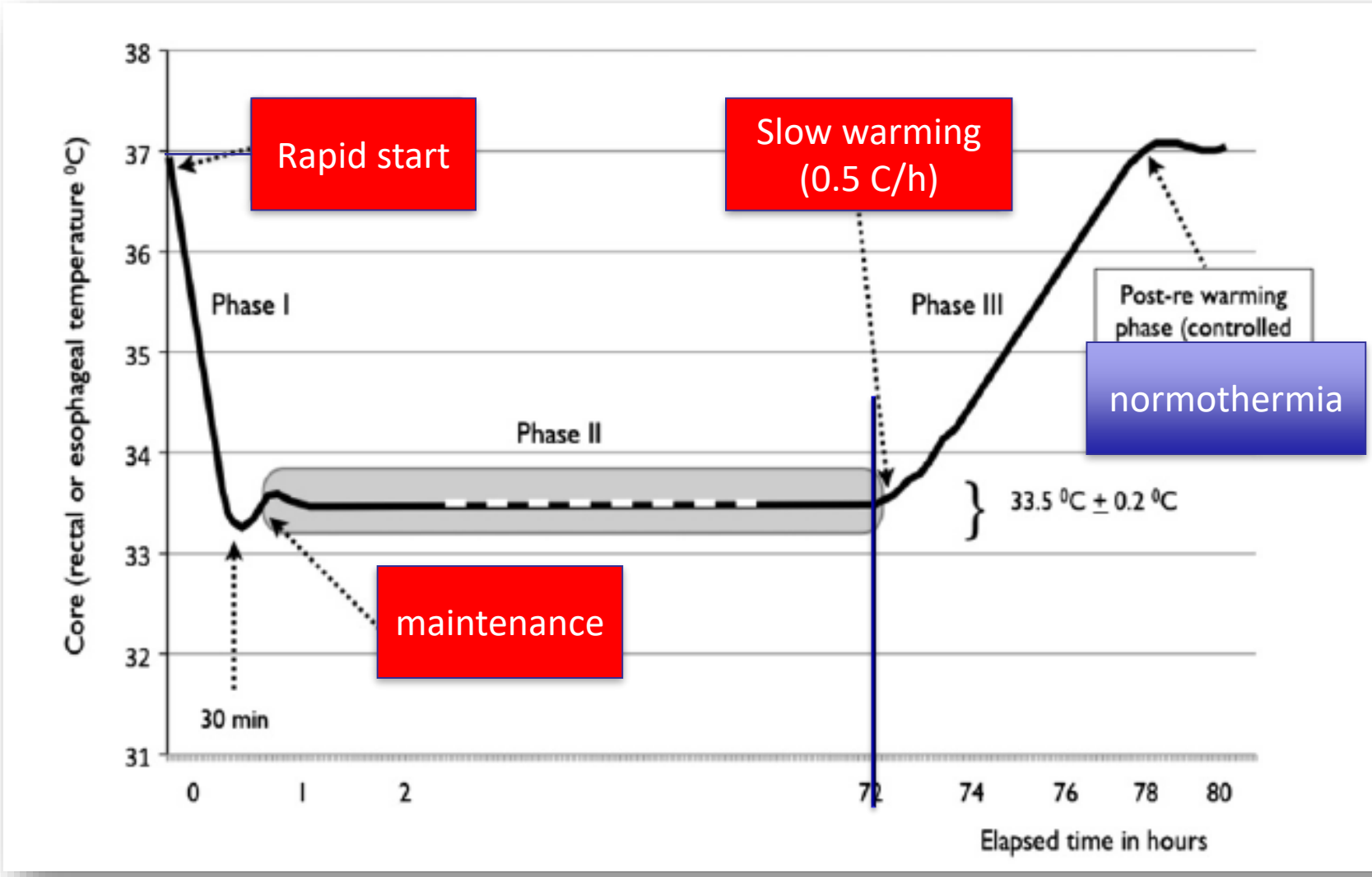
Pediatrics International (2016) **58**, 27–33 doi: 10.1111/ped.12747

Original Article

Comparison of selective head cooling versus whole-body cooling

Yalcın Celik,[1] Aytug Atıcı,[1] Selvi Gulası,[1] Cetin Okuyaz,[2] Khatuna Makharoblıdze[2] and Mehmet Ali Sungur[3]

[1]*Division of Neonatology, Department of Pediatrics, School of Medicine, Mersin University,* [2]*Department of Pediatric Neurology, and* [3]*Department of Biostatistics, School of Medicine, Mersin University, Mersin, Turkey*



Current hypothermia protocols have consistently involved starting treatment within the first 6 h of life, with systemic cooling to either 34.5 ± 0.5°C for head cooling, or 33.5 ± 0.5°C for whole-body cooling and continuing treatment for 48–72 h.

2013

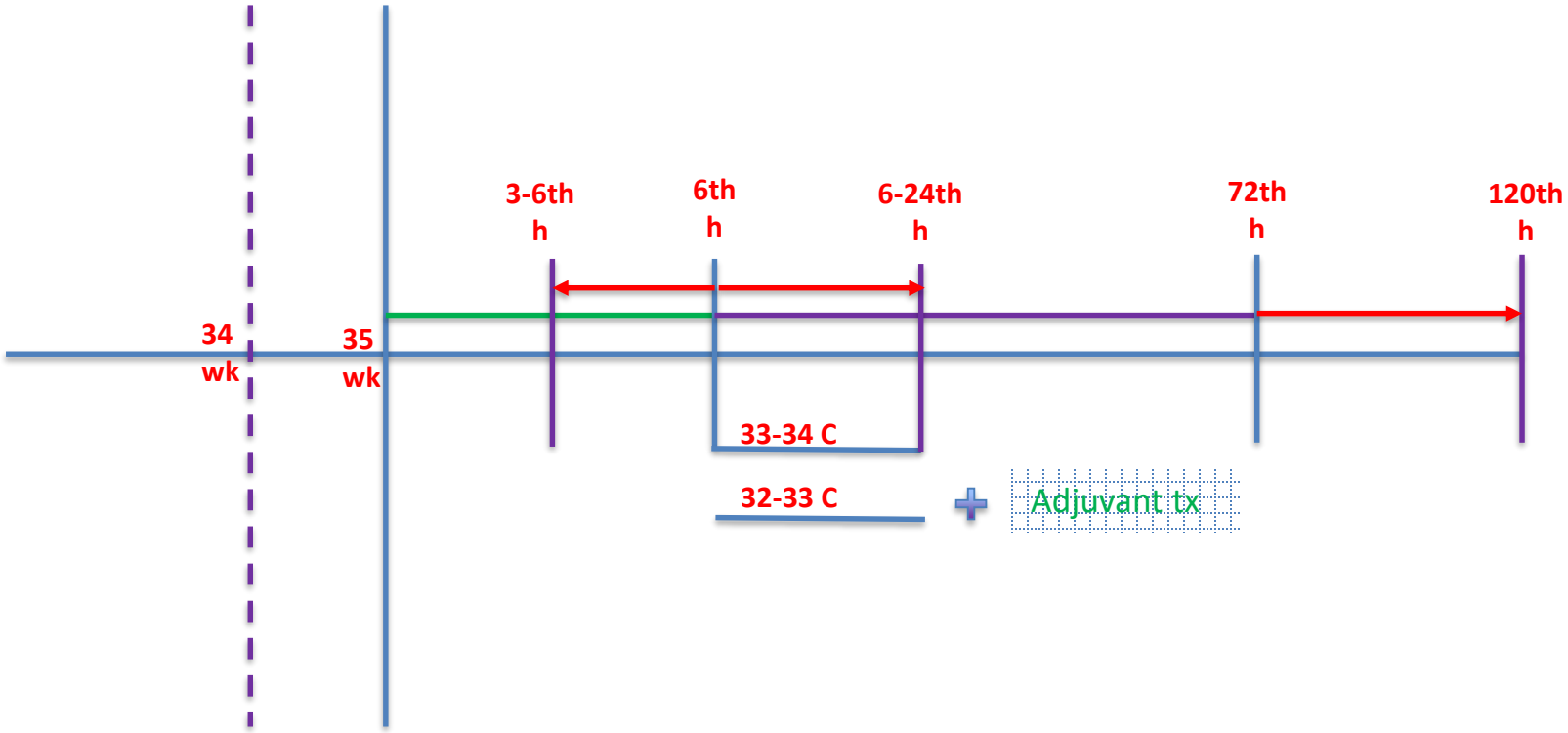
Cooling for newborns with hypoxic ischaemic encephalopathy.

Cochrane Database Syst Rev.

- 11 RCT, 1505 moderate/severe encephalopathy
- TH resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age (typical **RR 0.75,** NNTB 7)
- Cooling resulted in reductions in mortality (typical **RR 0.75**, NNTB 11) and in neurodevelopmental disability in survivors (typical **RR 0.77**, NNTB 8).
- Some adverse effects of hypothermia included an increase sinus **bradycardia** and a significant increase in **thrombocytopenia**.

AUTHORS' CONCLUSIONS:

- Hypothermia should be instituted in term and late preterm infants (>35 wk) with moderate-to-severe HIE **if identified before 6 h** of age.


3-6th h
6th h
6-24th h
72th h
120th h
34 wk
35 wk
33-34 C
32-33 C
Adjuvant tx

Published in final edited form as:
J Pediatr. 2017 April ; 183: 37–42. doi:10.1016/j.jpeds.2016.11.019.

Safety and Short-Term Outcomes of Therapeutic Hypothermia in Preterm Neonates 34–35 Weeks Gestational Age with Hypoxic-Ischemic Encephalopathy

Rakesh Rao, MD[*],
Assistant Professor of Pediatrics, Division of Newborn-Medicine, Washington University School of Medicine, 660 South Euclid, 8th Floor NWT, Campus Box 8116, St Louis, MO 63110

Results—Thirty-one preterm and 32 term neonates were identified. Therapeutic hypothermia-associated complications were seen in 90% of preterm infants and 81.3% of term infants (p=0.30). In the preterm infants, hyperglycemia (58.1% vs.31.3%, p=0.03) and rewarming before completion of therapeutic hypothermia (19.4% vs. 0.0%, p=0.009) were more likely compared with term infants. All deaths occurred in the preterm group (12.9% vs. 0%, p=0.04). Neuroimaging showed the presence of injury in 80.6% of preterm infants and 59.4% of term infants (p=0.07), with no differences in injury severity. Injury to the white matter was more prevalent in preterm infants compared with term infants (66.7% vs. 25.0%, p=0.001).

Conclusions—Therapeutic hypothermia in infants born at 34–35 weeks gestational age appears feasible. Risks of mortality and side effects warrant caution with use of therapeutic hypothermia in preterm infants.

When to cool?

- Clinical data suggested that asphyxiated infants who were able to be cooled within 3 h of birth had better motor outcomes than when hypothermia was started between 3 and 6 h.

- **However, hypothermia was only able to be started in 12% of infants within 4 h of birth in RCTs**

Neonatology (2013) **104**:228–33.

JAMA | Original Investigation

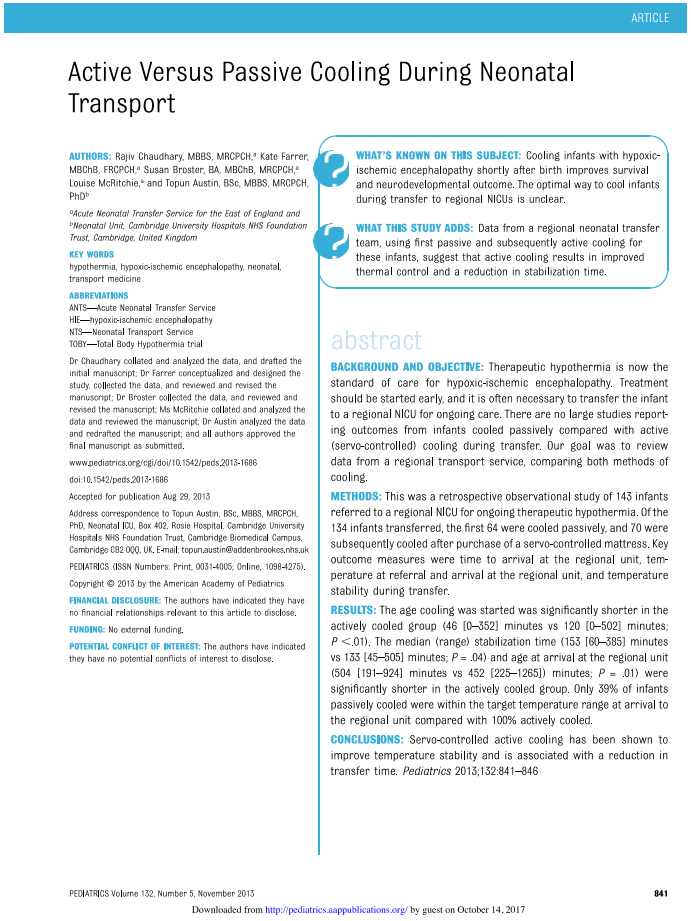
Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy

A Randomized Clinical Trial

Abbot R. Laptook, MD; Seetha Shankaran, MD; Jon E. Tyson, MD, MPH; Breda Munoz, PhD; Edward F. Bell, MD; Ronald N. Goldberg, MD; Nehal A. Parikh, DO, MS; Namasivayam Ambalavanan, MD; Claudia Pedroza, PhD; Athina Pappas, MD; Abhik Das, PhD; Aasma S. Chaudhary, BS, RRT; Richard A. Ehrenkranz, MD; Angelita M. Hensman, MS, RNC-NIC; Krisa P. Van Meurs, MD; Lina F. Chalak, MD, MSCS; Amir M. Khan, MD; Shannon E. G. Hamrick, MD; Gregory M. Sokol, MD; Michele C. Walsh, MD, MS; Brenda B. Poindexter, MD, MS; Roger G. Faix, MD; Kristi L. Watterberg, MD; Ivan D. Frantz III, MD; Ronnie Guillet, MD, PhD; Uday Devaskar, MD; William E. Truog, MD; Valerie Y. Chock, MD, MS-Epi; Myra H. Wyckoff, MD; Elisabeth C. McGowan, MD; David P. Carlton, MD; Heidi M. Harmon, MD, MS; Jane E. Brumbaugh, MD; C. Michael Cotten, MD, MHS; Pablo J. Sánchez, MD; Anna Maria Hibbs, MD; Rosemary D. Higgins, MD; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

CONCLUSIONS AND RELEVANCE Among term infants with hypoxic-ischemic encephalopathy, hypothermia initiated at 6 to 24 hours after birth compared with noncooling resulted in a 76% probability of any reduction in death or disability, and a 64% probability of at least 2% less death or disability at 18 to 22 months. Hypothermia initiated at 6 to 24 hours after birth may have benefit but there is uncertainty in its effectiveness.

Cooling on transport!



ARTICLE

Active Versus Passive Cooling During Neonatal Transport

AUTHORS: Rajiv Chaudhary, MBBS, MRCPCH,[a] Kate Farrer, MBChB, FRCPCH,[a] Susan Broster, BA, MBChB, MRCPCH,[a] Louise McRitchie,[a] and Topun Austin, BSc, MBBS, MRCPCH, PhD[a]

[a]*Acute Neonatal Transfer Service for the East of England and* [b]*Neonatal Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom*

KEY WORDS
hypothermia, hypoxic-ischemic encephalopathy, neonatal, transport medicine

ABBREVIATIONS
ANTS—Acute Neonatal Transfer Service
HIE—hypoxic-ischemic encephalopathy
NTS—Neonatal Transport Service
TOBY—Total Body Hypothermia trial

Dr Chaudhary collated and analyzed the data, and drafted the initial manuscript; Dr Farrer conceptualized and designed the study, collected the data, and reviewed and revised the manuscript; Dr Broster collected the data, and reviewed and revised the manuscript; Ms McRitchie collated and analyzed the data and reviewed the manuscript; Dr Austin analyzed the data and redrafted the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Cooling infants with hypoxic-ischemic encephalopathy shortly after birth improves survival and neurodevelopmental outcome. The optimal way to cool infants during transfer to regional NICUs is unclear.

WHAT THIS STUDY ADDS: Data from a regional neonatal transfer team, using first passive and subsequently active cooling for these infants, suggest that active cooling results in improved thermal control and a reduction in stabilization time.

abstract

BACKGROUND AND OBJECTIVE: Therapeutic hypothermia is now the standard of care for hypoxic-ischemic encephalopathy. Treatment should be started early, and it is often necessary to transfer the infant to a regional NICU for ongoing care. There are no large studies reporting outcomes from infants cooled passively compared with active (servo-controlled) cooling during transfer. Our goal was to review data from a regional transport service, comparing both methods of cooling.

METHODS: This was a retrospective observational study of 143 infants referred to a regional NICU for ongoing therapeutic hypothermia. Of the 134 infants transferred, the first 64 were cooled passively, and 70 were subsequently cooled after purchase of a servo-controlled mattress. Key outcome measures were time to arrival at the regional unit, temperature at referral and arrival at the regional unit, and temperature stability during transfer.

RESULTS: The age cooling was started was significantly shorter in the actively cooled group (46 [0–352] minutes vs 120 [0–502] minutes; $P < .01$). The median (range) stabilization time (153 [60–385] minutes vs 133 [45–505] minutes; $P = .04$) and age at arrival at the regional unit (504 [191–924] minutes vs 452 [225–1265]) minutes; $P = .01$) were significantly shorter in the actively cooled group. Only 39% of infants passively cooled were within the target temperature range at arrival to the regional unit compared with 100% actively cooled.

CONCLUSIONS: Servo-controlled active cooling has been shown to improve temperature stability and is associated with a reduction in transfer time. *Pediatrics* 2013;132:841–846

- Cooling infants with HIE shortly after birth improves survival and neurodevelopmental outcome.
- The optimal way to cool infants during transfer to regional NICUs is unclear.
- Data from a regional neonatal transfer team, using first passive and subsequently active cooling for these infants, suggest that **active cooling results in improved thermal control and a reduction in stabilization time**.

Active vs. passive cooling on transport

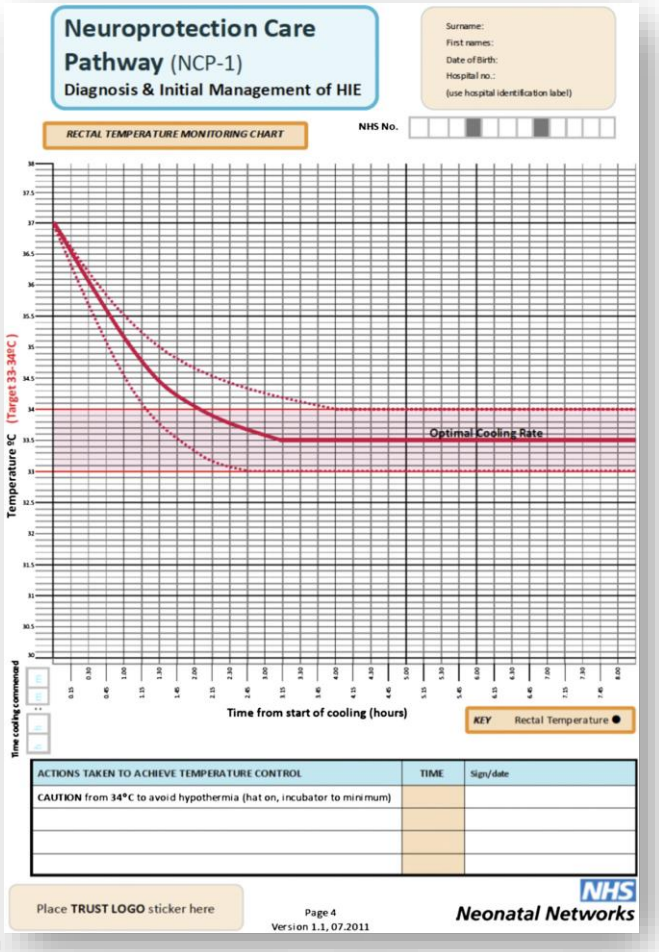
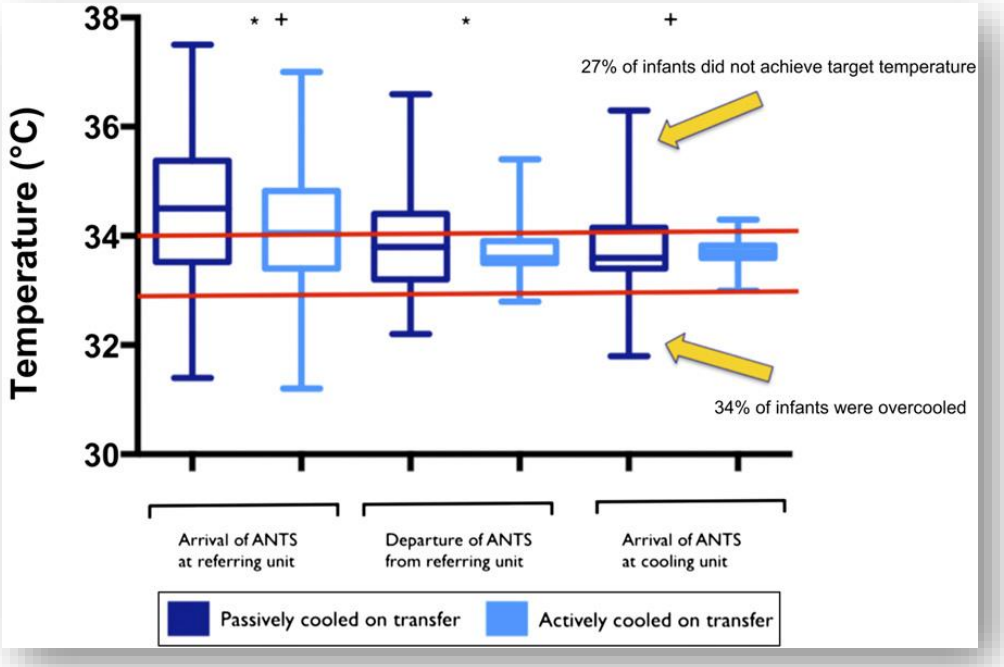


FIGURE 1
Page from the regional care pathway for the diagnosis and initial management of HIE. A temperature chart, devised for local units with the aim of achie controlled cooling with the use of passive methods, is depicted.



Active cooling results in better achieved targeted temperature on arrival to hospital (79% vs. 25%)

THERAPEUTIC HYPOTHERMIA AND TEMPERATURE MANAGEMENT
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Original Article

Therapeutic Hypothermia During Neonatal Transport: Active Cooling Helps Reach the Target

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Omer Erdeve

Duration and depth of the treatment?

- A recent experimental study extending the duration of cerebral cooling from 3 days until 5 days was not associated with any additional improvement in the recovery of EEG power.

- Consistent with this preclinical evidence, a large RCT of 72 h of hypothermia to 33.5°C compared with either prolonged hypothermia for 120 h or deeper cooling to 32°C, was stopped early because
  - **longer duration, lower temperature and the combination of longer duration and lower temperature were associated with a trend toward a higher risk of death in the neonatal period**

Cereb Blood Flow Metab (2015) **35**:751–8.
JAMA (2014) **312**:2629–39.

JAMA | Original Investigation

Effect of Depth and Duration of Cooling on Death or Disability at Age 18 Months Among Neonates With Hypoxic-Ischemic Encephalopathy
A Randomized Clinical Trial

Seetha Shankaran, MD; Abbot R. Laptook, MD; Athina Pappas, MD; Scott. A. McDonald, BS; Abhik Das, PhD; Jon E. Tyson, MD, MPH; Brenda B. Poindexter, MD, MS; Kurt Schibler, MD; Edward F. Bell, MD; Roy J. Heyne, MD; Claudia Pedroza, PhD; Rebecca Bara, RN, BSN; Krisa P. Van Meurs, MD; Carolyn M. Petrie Huitema, MS, CCRP; Cathy Grisby, BSN, CCRC; Uday Devaskar, MD; Richard A. Ehrenkranz, MD; Heidi M. Harmon, MD, MS; Lina F. Chalak, MD, MSCS; Sara B. DeMauro, MD, MSCE; Meena Garg, MD; Michelle E. Hartley-McAndrew, MD; Amir M. Khan, MD; Michele C. Walsh, MD, MS; Namasivayam Ambalavanan, MD; Jane E. Brumbaugh, MD; Kristi L. Watterberg, MD; Edward G. Shepherd, MD; Shannon E. G. Hamrick, MD; John Barks, MD; C. Michael Cotten, MD, MHS; Howard W. Kilbride, MD; Rosemary D. Higgins, MD; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

CONCLUSIONS AND RELEVANCE Among term neonates with moderate or severe hypoxic-ischemic encephalopathy, cooling for longer than 72 hours, cooling to lower than 33.5°C, or both did not reduce death or moderate or severe disability at 18 months of age. However, the trial may be underpowered, and an interaction was found between longer and deeper cooling. These results support the current regimen of cooling for 72 hours at 33.5°C.

Hypothermia in resource-limited settings

2014

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/siny

Review

Cooling in a low-resource environment: Lost in translation

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Keywords:
Therapeutic hypothermia
Low- and middle-income countries
Neonatal encephalopathy
Neonatal mortality

SUMMARY

Although cooling therapy has been the standard of care for neonatal encephalopathy (NE) in high-income countries for more than half a decade, it is still not widely used in low- and middle-income countries (LMIC), which bear 99% of the encephalopathy burden; neither is it listed as a priority research area in global health. Here we explore the major roadblocks that prevent the use of cooling in LMIC, including differences in population comorbidities, suboptimal intensive care, and the lack of affordable servo-controlled cooling devices. The emerging data from LMIC suggest that the incidence of coexisting perinatal infections in NE is no different to that in high-income countries, and that cooling can be effectively provided without tertiary intensive care and ventilatory support; however, the data on safety and efficacy of cooling are limited. Without adequately powered clinical trials, the creeping and uncertain introduction of cooling therapy in LMIC will be plagued by residual safety concerns, and any therapeutic benefit will be even more difficult to translate into widespread clinical use.

1. Introduction

Perinatal asphyxia associated with moderate to severe neonatal encephalopathy (NE) occurs at an approximate rate of 1–2 per 1000 live births in high-income countries [1] and 10–20 per 1000 live births in low- and middle-income countries (LMIC) [2]. Following moderate or severe encephalopathy, ~25–60% of the affected infants die and more than half of the survivors sustain significant brain injury and lifelong disability in LMIC [3]. Of the one million annual neonatal deaths caused by perinatal asphyxia, 99% occur in LMIC [4].

Therapeutic hypothermia has become the standard of care for NE in high-income countries following two decades of rigorous experimental and clinical research. This began with the demonstration of secondary energy failure and its amelioration with therapeutic hypothermia in animal models, followed by clinical trials, meta-analyses, registries, and finally its inclusion in national and international guidelines [5]. Therapeutic hypothermia reduces mortality after NE [typical relative risk (RR): 0.75; 95% confidence interval (CI): 0.64–0.88] and neurodisability in survivors at 18 months (typical RR: 0.77; 95% CI: 0.63–0.94) [6] and at school age (typical RR: 0.59; 95% CI: 0.37–0.94) [7,8]. Almost all eligible babies receive therapeutic hypothermia in the UK at present (~800 per year), and this is estimated to have saved the National Health Service a total of £125m since 2009 [9].

Given the simplicity of the intervention and the global disease burden, therapeutic hypothermia may have a considerable impact on the health and economies in LMIC. Unfortunately, in these settings the uptake of therapeutic hypothermia has been poor. Here we examine the various factors which have prevented the use of this highly effective therapy in settings which shoulder the greatest burden.

2. Issues related to healthcare infrastructure

2.1. Home deliveries and the lack of transport systems

In the 'standard model' of perinatal services practised in high-income countries, critically ill newborns are rapidly transported to resource-intensive tertiary neonatal units for therapeutic hypothermia – this is not readily applicable to the LMIC. In fact, such models are neither feasible nor desirable in LMIC, where simpler, affordable, and cost-effective interventions in primary and secondary care may be more effective in reducing neonatal mortality. In low-income countries in regions such as Sub-Saharan Africa, some communities have no access by road; communication systems are weak; many cannot afford private transport [10]; and many deliveries happen at home or in poorly equipped facilities [11]. Even in institutional deliveries, delayed maternity admissions

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- PA occurs at an approximate rate of 10–20 per 1000 live births in LMIC
- Of the one million annual neonatal deaths caused by PA, **99% occur in LMIC**.
- Benefit of therapeutic hypothermia may be far higher in LMIC than in high-income countries, considering the disease burden.
- Adequately powered clinical trials are required to ensure that cooling is indeed safe and effective in LMIC neonatal units (HELIX trial NCT01760629).

2015

THE JOURNAL OF PEDIATRICS • www.jpeds.com COMMENTARY

Neuroprotection for Perinatal Hypoxic Ischemic Encephalopathy in Low- and Middle-Income Countries

Mohamed Tagin, MB, BCh[1], Hesham Abdel-Hady, PhD[2], Sajjad ur Rahman, MBBS, DCH, MCPS, FCPS, FRCPCH[3,4], Denis V. Azzopardi, FRCPCH[5], and Alistair J. Gunn, MBChB, PhD[6]

Perinatal hypoxic ischemic encephalopathy (HIE) is associated with approximately one-quarter of global neonatal deaths.[1] In 2010, there were an estimated 1.15 million cases of neonatal encephalopathy, of which 96% of were from low- and middle-income (LMI) countries.[2] In the developed world, therapeutic hypothermia is now widely accepted as the standard of care for treating newborns with moderate to severe HIE.[3] Therapeutic hypothermia has been found to reduce the risk of death or major neurodevelopmental disability at age 18 months (risk ratio [RR], 0.76; 95% CI, 0.69-0.84) and to increase survival with normal neurologic function (RR, 1.63; 95% CI, 1.36-1.95).[4,5] Recent studies have confirmed improved neurocognitive outcomes at school age.[6,7] Those studies involved predominantly developed countries. In contrast, a systematic review of 7 trials including 567 newborns from LMI countries, using mainly low-cost cooling techniques, did not show a significant reduction in neonatal mortality (RR, 0.74; 95% CI, 0.44-1.25).[8] Although the point estimate is consistent with estimates from the developed world,[4,5] the wide CI of that result means that a clinically important benefit or harm could not be excluded. Furthermore, there was insufficient long-term follow-up to allow assessment of whether hypothermia had improved neurodevelopmental outcomes.

See related article, p 58

The heterogeneity of outcomes in studies from LMI countries may be an artifact of poorly designed studies, many of which were very small.[8] The largest study in that review, which carried almost one-half of the weight in the primary outcome (neonatal mortality), may have introduced selection bias by including more boys (85%) and violated its protocol by including 20% cases with mild encephalopathy.[9] Overall, 15% of the patients in these studies had mild encephalopathy, and, consistent with this, only 12% required ventilation.[8] Newborns with mild HIE have a low risk of mortality,[10] reducing the study's power and potentially leading to a false conclusion that the intervention is not conclusive when the intervention was not applied to the correct target population. It is unclear whether the low frequency of mechanical ventilation reflects only selection for milder cases, or whether resource limitations constrained care.

Alternatively, the heterogeneity of outcomes potentially could be "real," that is, related to medical factors that impair the effectiveness of hypothermia. First, there may be biological differences in the study populations. Some evidence from a newborn rat model of hypoxic ischemic brain injury suggests that priming with infection before the injury may reduce the protective effect of mild hypothermia.[11] The rate of perinatal neonatal sepsis is higher in many LMI countries,[12] and thus might reduce the neuroprotection afforded by hypothermia. However, as reviewed recently, the rate of confirmed sepsis in Ugandan or Indian infants with encephalopathy is not materially different from that reported in recent developed world trials.[13] Second, the time of the insult before treatment is critical to the effectiveness of hypothermia,[14] and is often difficult to quantify. In LMI countries, a higher proportion of perinatal brain injury may be related to chronic antenatal insults, such as malnutrition and intrauterine growth restriction,[15] and there are often delays in providing care owing to a limited medical and nursing infrastructure.[16] Thus, in many cases, the therapeutic window may have passed by the time that treatment could be initiated.[17] Third, low-resourced or less-experienced centers may be less rigorous in using therapeutic hypothermia according to established protocols, or may use less rigorous selection criteria, which would reduce the apparent efficacy of hypothermia or increase complications.[18,19] Fourth, such countries may not be able to provide adequate neonatal intensive care, including proper monitoring, mechanical ventilation, sedation, and use of oxygen. Finally, LMI countries may be less able to afford approved devices to induce stable hypothermia within targeted goals. Nevertheless, low-cost alternative devices, such as servo-controlled fans to blow room air, ice packs, cold water bottles, mattresses made of phase-changing materials, and less expensive servo-controlled cooling blankets, are being developed.[18,20-23]

This outcome leaves LMI countries with insufficient evidence that therapeutic hypothermia is safe and protective in their current settings, and yet it is almost certainly no longer acceptable to undertake trials of hypothermia against normothermia. This ethical conundrum is not unique, and it

HIE	Hypoxic ischemic encephalopathy
LMI	Low- and middle-income
RR	Risk ratio

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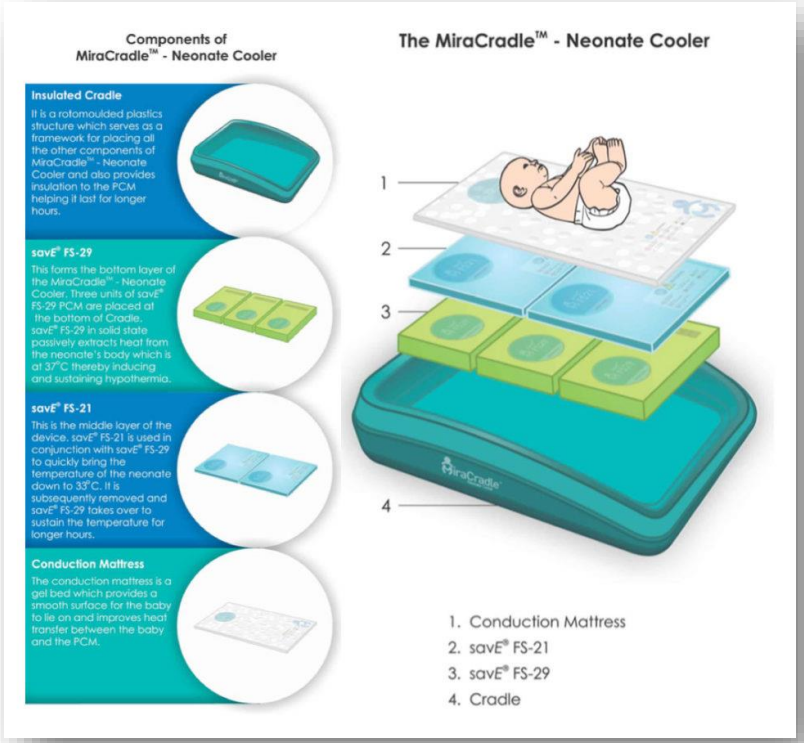
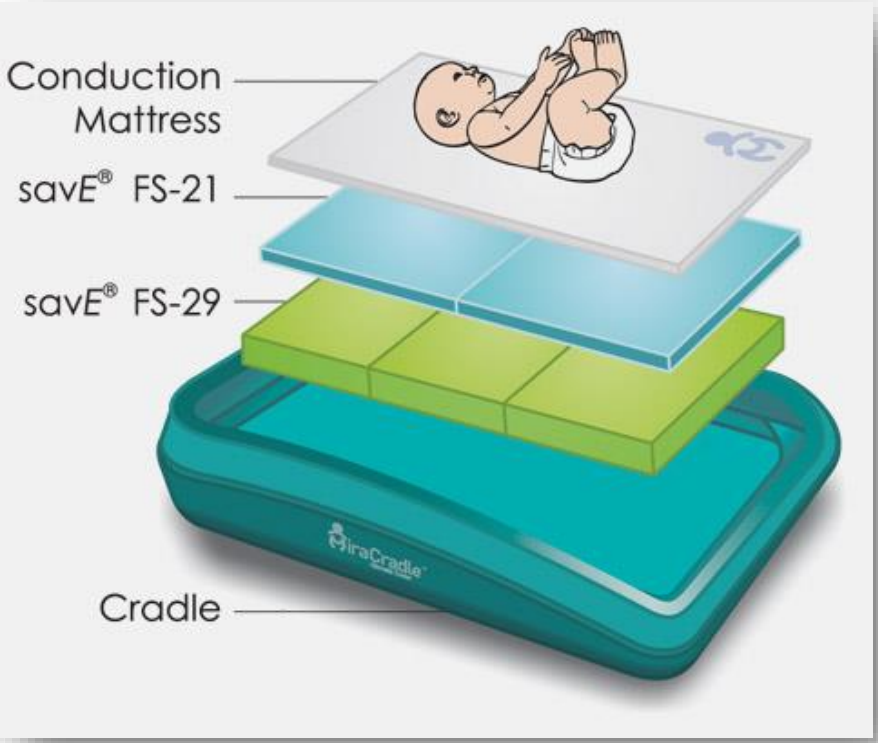
The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.02.056

- The rate of confirmed **sepsis is higher** in LMICs
- There are often **delays in providing care** owing to a limited medical and nursing infrastructure
- Low- resourced or **less-experienced centers** may be less rigorous in using therapeutic hypothermia according to established protocols
- Such countries may **not be able to provide adequate neonatal intensive care**, including proper monitoring, mechanical ventilation, sedation, and use of oxygen.
- LMI countries may be **less able to afford approved devices** to induce stable hypothermia within targeted goals.

Omer Erdeve


Components of
MiraCradle™ - Neonate Cooler
Insulated Cradle
It is a rotomoulded plastics structure which serves as a framework for placing all the other components of MiraCradle™ - Neonate Cooler and also provides insulation to the PCM helping it last for longer hours.
savE® FS-29
This forms the bottom layer of the MiraCradle™ - Neonate Cooler. Three units of savE® FS-29 PCM are placed at the bottom of Cradle. savE® FS-29 in solid state passively extracts heat from the neonate's body which is at 37°C thereby inducing and sustaining hypothermia.
savE® FS-21
This is the middle layer of the device. savE® FS-21 is used in conjunction with savE® FS-29 to quickly bring the temperature of the neonate down to 33°C. It is subsequently removed and savE® FS-29 takes over to sustain the temperature for longer hours.
Conduction Mattress
The conduction mattress is a gel bed which provides a smooth surface for the baby to lie on and improves heat transfer between the baby and the PCM.
The MiraCradle™ - Neonate Cooler
1
2
3
4
1. Conduction Mattress
2. savE® FS-21
3. savE® FS-29
4. Cradle


Conduction Mattress
savE® FS-21
savE® FS-29
Cradle

Indian Pediatr. 2018 Mar 15;55(3):201-205. Epub 2017 Dec 14.

Phase Changing Material for Therapeutic Hypothermia in Neonates with Hypoxic Ischemic Encephalopathy - A Multi-centric Study.

Thomas N[1], Abiramalatha T[2], Bhat V[3], Varanattu M[4], Rao S[5], Wazir S[6], Lewis L[7], Balakrishnan U[8], Murki S[9], Mittal J[10], Dongara A[11], Prashantha YN[12], Nimbalkar S[13].

Author information

Abstract

OBJECTIVE: To assess the feasibility and safety of cooling asphyxiated neonates using phase changing material based device across different neonatal intensive care units in India.

DESIGN: Multi-centric uncontrolled clinical trial.

SETTING: 11 level 3 neonatal units in India from November 2014 to December 2015.

PARTICIPANTS: 103 newborn infants with perinatal asphyxia, satisfying pre-defined criteria for therapeutic hypothermia.

INTERVENTION: Therapeutic hypothermia was provided using phase changing material based device to a target temperature of 33.5±0.5oC, with a standard protocol. Core body temperature was monitored continuously using a rectal probe during the cooling and rewarming phase and for 12 hours after the rewarming was complete.

OUTCOME MEASURES: Feasibility measure - Time taken to reach target temperature, fluctuation of the core body temperature during the cooling phase and proportion of temperature recordings outside the target range. Safety measure - adverse events during cooling.

RESULTS: The median (IQR) of time taken to reach target temperature was 90 (45, 120) minutes. The mean (SD) deviation of temperature during cooling phase was 33.5 (0.39) ºC. Temperature readings were outside the target range in 10.8% (5.1% of the readings were <33oC and 5.7% were >34oC). Mean (SD) of rate of rewarming was 0.28 (0.13)oC per hour. The common adverse events were shock/ hypotension (18%), coagulopathy (21.4%), sepsis/probable sepsis (20.4%) and thrombocytopenia (10.7%). Cooling was discontinued before 72 hours in 18 (17.5%) babies due to reasons such as hemodynamic instability/refractory shock, persistent pulmonary hypertension or bleeding. 7 (6.8%) babies died during hospitalization.

CONCLUSIONS: Using phase changing material based cooling device and a standard protocol, it was feasible and safe to provide therapeutic hypothermia to asphyxiated neonates across different neonatal units in India. Maintenance of target temperature was comparable to standard servo-controlled equipment.

Complications

	studies / number of participants	
Arrythmia	5 / 806	4.08 (1.55, 10.74)
Hypotension	8 / 1108	1.03 (0.93, 1.13)
Coagulopathy	7 / 1114	0.96 (0.80, 1.15)
Thrombocytopenia	4 / 638	1.28 (1.07, 1.52)
Seizure after enrolment	8 / 1102	0.96 (0.86, 1.06)
Renal failure	5 / 310	0.95 (0.53, 1.70)
Hepatic side effects	5 / 678	0.85 (0.69, 1.04)
Infection	7 / 544	0.86 (0.40, 1.88)
Pulmonary hypertension	5 / 636	1.36 (0.95, 1.96)

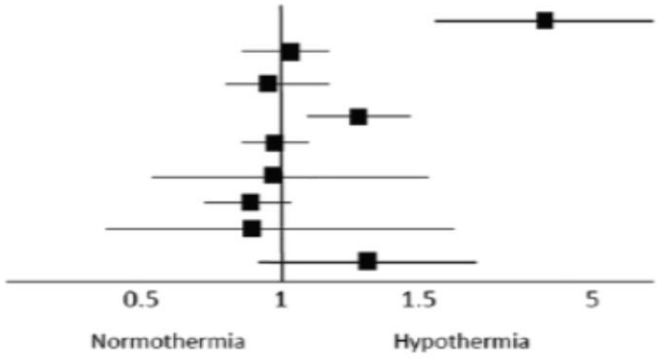
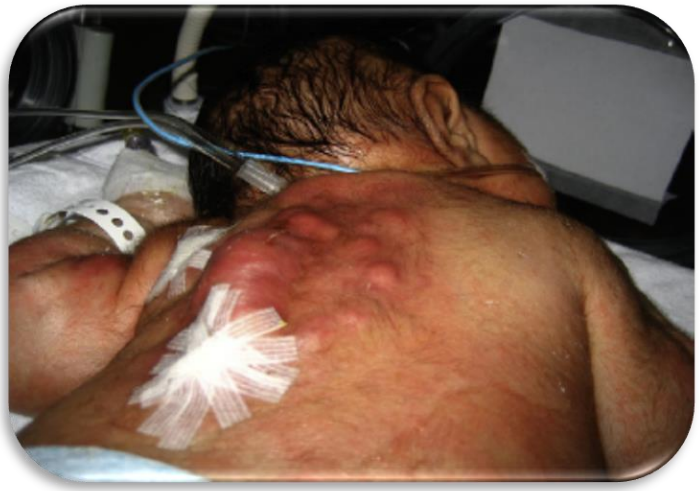
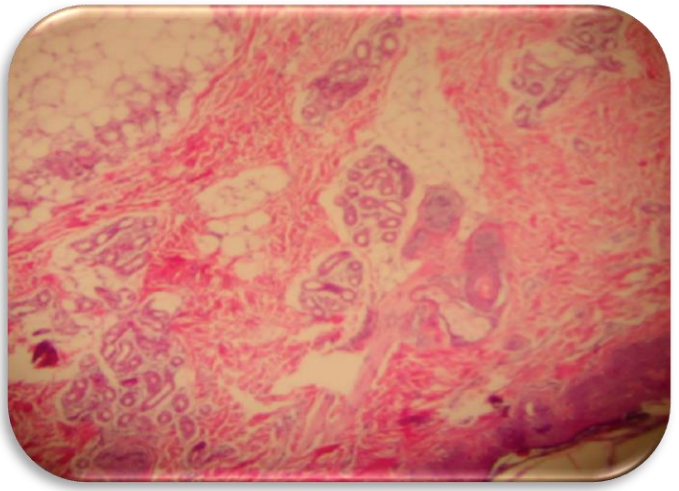


Fig. 4. Safety outcomes.





Pediatric Hematology and Oncology, 30:246–252, 2013

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DOI: 10.3109/08880018.2013.771240

informa
healthcare

HEMATOLOGY IN INFANTS

The Effect of Whole-Body Cooling on Hematological and Coagulation Parameters in Asphyxic Newborns

Mehmet Yekta Oncel,[1] Omer Erdeve,[2] Erhan Calisici,[1] Serife Suna Oguz,[1] Fuat Emre Canpolat,[1] Nurdan Uras,[1] and Ugur Dilmen[1,3]

Pediatric Dermatology Vol. 30 No. 1 120–123, 2013

Hypercalcemia Due to Subcutaneous Fat Necrosis in a Newborn After Total Body Cooling

Ahmet Akcay, M.D., Melek Akar, M.D., M. Yekta Oncel, M.D., Avidan Kızılelma, M.D., Omer Erdeve, M.D., S. Suna Oguz, M.D., Nurdan Uras, M.D., and Ugur Dilmen, M.D.

Case Reports in Pediatrics
Volume 2013, Article ID 254089, 3 pages
http://dx.doi.org/10.1155/2013/254089

Case Report

A Neonate with Subcutaneous Fat Necrosis after Passive Cooling: Does Polycythemia Have an Effect?

Erhan Calisici,[1] Mehmet Yekta Oncel,[1] Halil Degirmencioglu,[1,2] Gonca Sandal,[3] Fuat Emre Canpolat,[1] Omer Erdeve,[4] Serife Suna Oguz,[1] and Ugur Dilmen[1,5]

FIGURE 1: Macroscopic appearance of SCFN in our patient.

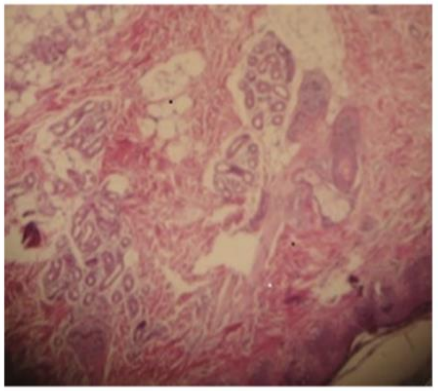
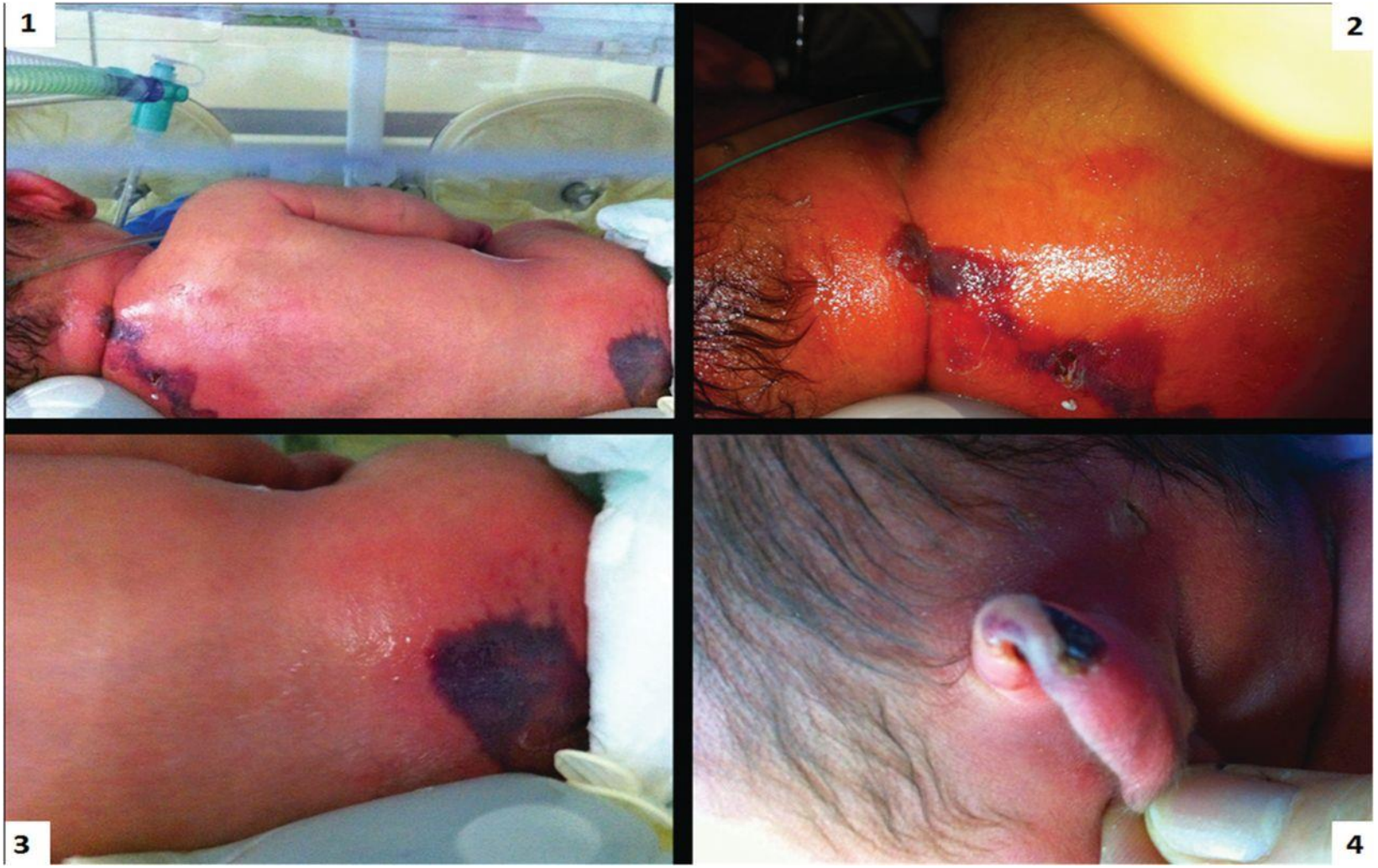


FIGURE 2: Microscopic appearance of SCFN showing the presence of adipocytes with eosinophilic cytoplasms and histiocytes infiltrating between them.

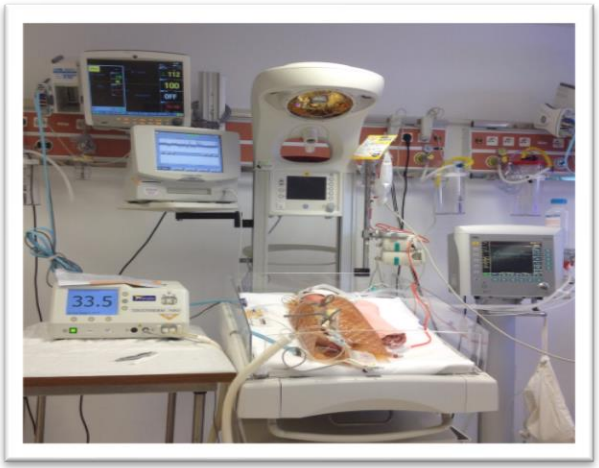
Erythematous, bullous, necrotic lesions were detected on the lumbosacral, cervical regions and the auricula of the ears.



Gamze Demirel et al. Arch Dis Child Fetal Neonatal Ed 2013;98:F150-F151

Ankara University Children's Hospital NICU last 5 years series:

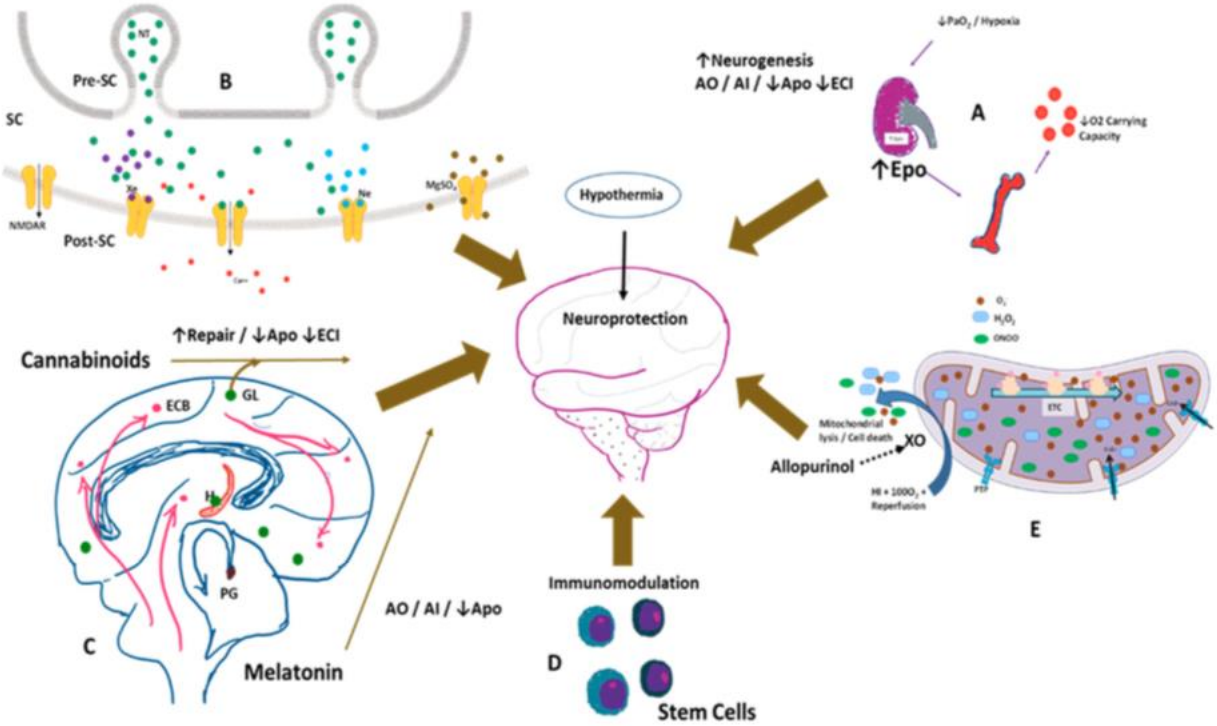
- 2012-2017
- 45 patients (24 inborn)
- 6 deaths
- Survival %87



What about hypothermia in patients on ECMO run!

Table 1. Promising therapies in management of HIE by mechanism.

Mechanism	Clinical Trials	Pre-Clinical Studies
Endogenous	Erythropoietin, darbepoietin Stem cells Melatonin	Remote ischemic postconditioning Endocannabinoids
Exogenous	Monosialogangliosides Xenon Allopurinol Topiramate Magnesium sulfate	Argon Azithromycin



Potential most effective neurotrophic treatment: Mesenchymal stem cell

- MSC treatment:
  - BMSC: Ferroni (2013), Taran (2014)
  - **UCB-MSC:** Dalous (2012), Xia (2010)
    - ✓Easily obtained
    - ✓No damage to donor
    - ✓More immature cells
    - ✓No ethical problem and somatic mutation risks
    - ✓Low tumor risk potency
    - ✓Low GVHD risk

Int. J. Devl Neuroscience 38 (2014): 147–154

- **UCB-MSC:**
  - Allogenic: So Yoon An (2015)
  - Autologous: Cotton (2014)
- Questions:
  - Administration way (intraventricular/iv)
  - Dose ($1x10^6$-$5x10^5$ cell)
  - Timing (as soon as possible)
  - Long term safety
- **DCC-Milking (?)**

In order to optimize the potential of this treatment, systematic preclinical studies of the mechanisms of action, and clinical studies on optimal dosing and timing, and type of stem cells are now needed.

J Pediatr 2014; 164: 973
Neonatology 2016; 109: 377

Take home messages

- ✓ Asphyxia is still common, even in developed countries but more in LMICs
- ✓ Not all encephalopathies after birth are due to PA
- ✓ Neuroimaging and neurophysiological techniques have limitations and there is no specific biomarker defined
- ✓ Hypothermia should be started as soon as possible. Think about passive/active cooling on transport!
- ✓ Therapeutic hypothermia is the only proven treatment but is not a golden bullet. There is a need for adjunctant treatment, preferably a cheap one (erythropoietin ?!)
- ✓ Mesenchymal stem cell transplantation is a promising future treatment choice for HIE for prevention of CP
- ✓ Adequate rescuscitation, targeted oxygen use, preventing hyperthermia and hypoglycemia, initiating passive/active coolingat referring center, therapeutic hypothermia with servo-controlled device or phase changing materias/frozen gel packs should be main aims in treatment for resource-limited settings

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