The Role of Respiratory Care in the Neurologically Devastated Infant

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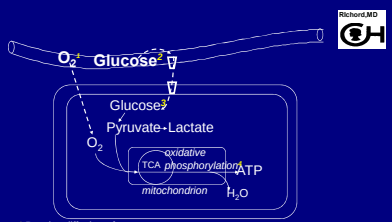
Objectives

- Understand the physiological consequences of birth asphyxia and the pathophysiology of resultant Hypoxic Ischemic Encephalopathy (HIE)
- Gain knowledge regarding advances in treatment options for HIE
- Develop an appreciation for the important role that respiratory therapists play in minimizing adverse outcomes in HIE patients
- Appreciate how HIE interventions effect lab values
- Examine the relationship between HIE interventions and persistent pulmonary hypertension (PPHN)

How does the brain metabolize energy?



-*1* Passive diffusion of oxygen
- *2* Facilitated transport of glucose via transporters that are compartmentally specialized and developmentally regulated, and use-dependent
- *3* Little/no glucose stores
- *4* Virtually all oxidative metabolism (limited capacity for anaerobic metabolism)

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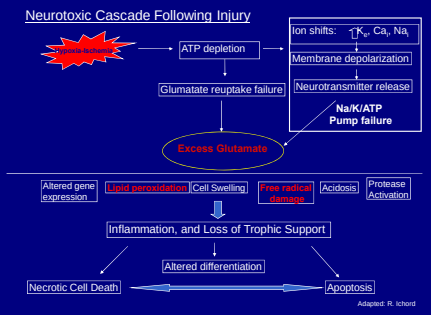
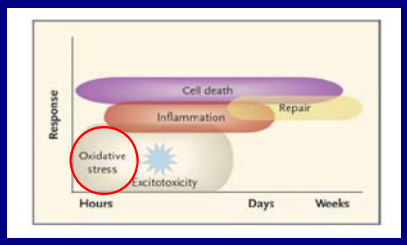
What happens to the asphyxiated newborn?

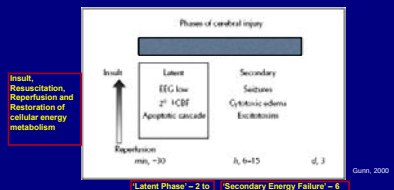


How does the immature brain respond to injury?



Ferriero, NEJM 2004; 351: 1985-95

Two phases of injury



Insult, Resuscitation, Reperfusion and Restoration of cellular energy metabolism

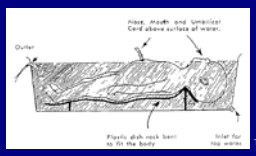
'Latent Phase' ~ 2 to 6 hrs post injury, brief period of normal cerebral energy metabolism

'Secondary Energy Failure' ~ 6 to 15 hrs post injury, ↓ in ATP, ↑ lactate; associated with poor neurodevelopmental outcome

Dry, Why is this important??!?!?

History

- Westin et al. (1959)
  - Infants with 'neonatal asphyxia pallida' who were unresponsive at birth were cooled in tub of cool water until respirations resumed (2 to 14 min, rectal temp 25-33°C). Infants rewarmed passively. Improved neurologic outcomes.



Thoresen, 2000

History

- Kopchev (1985)
  - Selective head cooling for asphyxiated infants using cool shower then cap until rectal temperature reached 30°C

Thoresen, 2000

History

CoolCap trial

First randomized controlled trial to Investigate the potential benefits of cooling Asphyxiated neonates. Results demonstrated that cooling toA rectal temperature of 34 – 35 degrees Celsius within 6Hours of delivery resulted in improved neurological outcomes

Natus, Olympic Medical

Selway L. Hypoxic ischemic encephalopathy and hypothermic intervention for neonates. *Adv Neonatal Care* 2010; **10(2)**: 60-6.

Present

ORIGINAL ARTICLE

Whole-Body Hypothermia for Neonates with Hypoxic–Ischemic Encephalopathy

Seetha Shankaran, M.D., Abbot R. Laptook, M.D., Richard A. Ehrenkranz, M.D., Jon E. Tyson, M.D., M.P.H., Scott A. McDonald, B.S., Edward F. Donovan, M.D., Avroy A. Fanaroff, M.D., W. Kenneth Poole, Ph.D., Linda L. Wright, M.D., Rosemary D. Higgins, M.D., Neil N. Finer, M.D., Waldemar A. Carlo, M.D., Shahnaz Duara, M.D., William Oh, M.D., C. Michael Cotten, M.D., David K. Stevenson, M.D., Barbara J. Stoll, M.D., James A. Lemons, M.D., Ronnie Guillet, M.D., Ph.D., and Alan H. Jobe, M.D., Ph.D., for the National Institute of Child Health and Human Development Neonatal Research Network*

CONCLUSIONS

Whole-body hypothermia reduces the risk of death or disability in infants with moderate or severe hypoxic–ischemic encephalopathy.

Summerlin Hospital Medical Center

Present

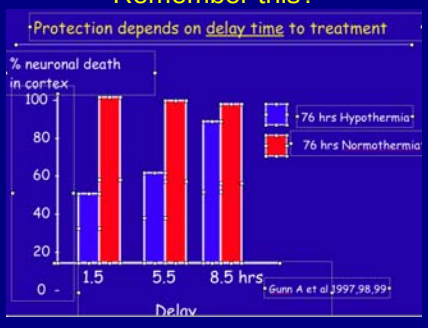
- Infants >/= 36 weeks gestation
- Cord pH < 7.0 / Base deficit >/= 16 mmol
- Cord pH 7.01 - 7.15 / Base deficit 10 - 15.9 mmol AND
- Acute perinatal event OR
- 10 minute Apgar </= 5 OR
- Assisted ventilation at birth for at least 10 minutes

•AND

One or more signs in 3 of the following categories

NEJM 2005; 353: 1574-1584

Remember this?



The Role of the Respiratory Therapist

Oxygenation

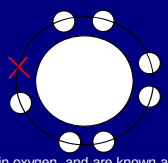
Ventilation

Oxygen and the Brain

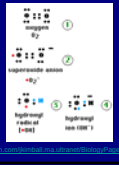
Oxygen and the Brain

Free Radicals

- Free Radical : Cluster of atoms, one of which contains an unpaired electron (red) in it's outermost shell



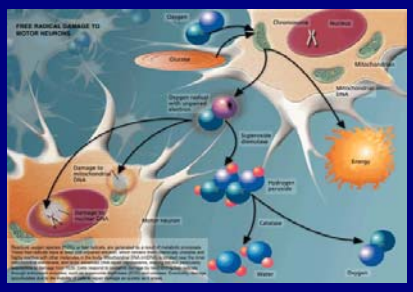
- Most biological free radicals contain oxygen, and are known as Reactive Oxygen Species (ROS)



http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/R/ROS.html

Oxygen and the Brain

How free radicals do their damage



http://www.als.ca/if_you_have_als/images/damaged-cells.gif

Oxygen and the Brain

Why the brain is at particular risk

- Brain contains a large proportion of polyunsaturated lipids
- Lipid peroxidation

- Brain relies almost entirely on aerobic metabolism
- increased risk of reactive oxygen species leaking from cell membranes

- Following ischemia, period of reperfusion/reoxygenation
- Hypoxanthine combines with oxygen in the presence of xanthine oxidase to produce free radicals

Wheeler D, Wong J, Shanley T. Oxidative damage in acute brain injury. *Pediatric critical care medicine basic science and clinical evidence*. New York: Springer, 2007:877

Oxygen and the Brain

Pediatr Res. 2006 Mar;59(3):423-7.
Impact of room air resuscitation on early growth response gene-1 in a neonatal piglet model of cerebral hypoxic ischemia.
Tyree MM, Dalgard C, O'Neill JT.
Department of Pediatrics, Uniformed Services University of the Helath Sciences, Bethesda, MD 20814, USA.

- Early growth response gene-1 (Egr-1) is up-regulated by hypoxia-ischemia (HI) and reactive oxygen species (ROS)
- Hypothesized resuscitation from HI with 100% O2 would increase Egr-1 expression, ROS, and cell death
- Piglets underwent carotid artery occlusion and breathed 8-12% O2 for 1 h followed by 21% or 100% for 1 h
- No significant difference initially in Egr-1, or ROS...BUT...
- 100% O2 administration was associated with increased cell death in the brainstem independent of HI
- Concluded100% O2 may be toxic to brainstem cells with potential significance for long-term outcome

Oxygen and the Brain

Resuscitation. 2008 Apr;77(1):111-20. Epub 2008 Feb 20.
Persistent neurochemical changes in neonatal piglets after hypoxia-ischemia and resuscitation with 100%, 21% or 18% oxygen.
Jantzie LL, Cheung PY, Obaid L, Emara M, Johnson ST, Bigam DL, Todd KG.
Neurochemical Research Unit, Department of Psychiatry, 1E7 Walter Mackenzie Centre, University of Alberta, Edmonton, Alberta, Canada T6G 2R7.

- Changes in neurotransmitters and amino acids associated with HI and cell death
- Hypothesized lower FiO2 should decrease changes in neurotransmitters and amino acids
- Newborn piglets underwent carotid artery occlusion and resuscitated w/ 18, 21, or 100% O2
- Resuscitation with 100% oxygen significantly increased glutamate in dorsal cortex
- Concluded Degree of change in neurotransmitters and amino acids may be influenced by O2

Oxygen and the Brain

J Neurosci Res. 2008 Dec;86(16):3584-604.
Bax shuttling after neonatal hypoxia-ischemia: hyperoxia effects.
Gill MB, Bockhorst K, Narayana P, Perez-Polo JR.
Department of Neuroscience and Cell Biology, University of Texas-Medical Branch, Galveston, TX 77555-1072, USA.

- BcL-2 associated X protein (Bax) trigger of cell death signaling cascade after HI
- Investigation of hyperoxia's effect on Bax expression
- T-2 weighted MRI of rats resuscitated with 100% O2 showed increased lesion activity
- Data suggests 100% O2 increased Bax-mediated activation of cell death signaling & lesion volume

Oxygen and the Brain

PEDIATRICS Vol. 107 No. 4 April 2001, pp. 642-647
Resuscitation With Room Air Instead of 100% Oxygen Prevents Oxidative Stress in Moderately Asphyxiated Term Neonates
Received Mar 28, 2000; accepted Aug 9, 2000.
Máximo Vento*, Miguel Asensi, Juan Sastre, Fernando García-Sala*, Federico V. Pallardó, and José Viña

- Reduced-to-oxidized-glutathione ratio(OxR) - accurate index of oxidative stress
- Term neonates with moderate asphyxia resuscitated with 100% or 21%
- 21% group showed quicker recovery based on Apgar, time to cry, and sustained respiration
- OxR lower in 100% group (meaning increased oxidation)
- Increased oxidative stress in 100% group despite increased antioxidant activity
- 100% group showed prolonged oxidative stress, even after 4 weeks of life

Ventilation and the Brain

Ventilation and the Brain

Crit Care Med. 2010 May;38(5):1348-59.
Hypocapnia and the injured brain: more harm than benefit.
Curley G, Kavanagh BP, Laffey JG.
Department of Anaesthesia, University College Hospital, Galway, Ireland.

- Review of hyperventilation practices
- Long-term benefit of hyperventilation is not well documented, and based mostly on experience
- Hypocapnia can exacerbate cerebral ischemia (cerebral vasoconstriction)
- Subsequent normocapnia can cause rebound cerebral hyperemia

Ventilation and the Brain

Neonatology. 2007;91(1):20-7. Epub 2007 Nov 10.
Effects of severe hypocapnia on expression of bax and bcl-2 proteins, DNA fragmentation, and membrane peroxidati products in cerebral cortical mitochondria of newborn piglets.
Lopez Pinto A, Fritz KI, Ashraf QM, Mishra OP, Delivoria-Papadopoulos M.
Division of Pulmonology, Department of Pediatrics, University of Maryland, Baltimore, MD 21201 , USA.

- Hypocapnia may result in neuronal and mitochondrial alterations increasing cell deatth signaling
- Hypothesized that hypocapnia may increase pro-apoptotic protein Bax, DNA fragmentation, and cellular membrane lipid peroxidation
- Normoxic piglets: Hypocapnic (11 - 15 mmHg) vs Normocapnic (40 mmHg) and corrected normocapnic
- Ratio of Bax/BcL-2 significantly increased in hypocapnic group
- Mitochondrial DNA fragmentation increased in hypocapnic group
- Cellular membrane lipid peroxidation increased in hypocapnic group

Ventilation and the Brain

Pediatr Res. 1997 Jul;42(1):24-9.
Effect of carbon dioxide on cerebral metabolism during hypoxia-ischemia in the immature rat.
Vannucci RC, Brucklacher RM, Vannucci SJ.
Department of Pediatrics (Pediatric Neurology), The Pennsylvania State University College of Medicine, The Milton S. Hershey Medical Center, Hershey 17033-0850, USA.

- 7 day postnatal rats subjected to hypoxia-ischemia
- Hypo (0.3% CO2/3.5 kPa) Normo(6% CO2/5.1 kPa) or Hyper(8% CO2/7.3 kPa) -capnic
- CBF during HI better maintained by normo- and hyper- capnic groups
- Brain glucose higher and lactate lower in normo- and hyper- capnic group
- Metabolism occurred aerobically in normo- and hyper- capnic groups rather than anaerobically
- Cerebrospinal fluid glutamate concentration lower in hypercapnic group

Ventilation and the Brain

A word of caution

Hypercapnia **NOT** extreme hypercapnia

Pediatr Res. 2001 Jun;49(6):799-803.
Effect of extreme hypercapnia on hypoxic-ischemic brain damage in the immature rat.
Vannucci RC, Towfighi J, Brucklacher RM, Vannucci SJ.
Departments of Pediatrics (Pediatric Neurology), The Pennsylvania State University College of Medicine, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033-0850, USA. rvannucci@psu.edu

- Ascertain the effect of **extreme** hypercapnia on HI brain damage
- 7-day postnatal rats exposed for 2 hours to:
- 3% CO2 - normocapnia
- 12% CO2 - moderate hypercapnia
- 15% Co2 - severe hypercapnia
- 30 day neurological examination showed that those rats exposed to 12% CO2 were neither less nor more brain damaged than the normocapnic group
- The 15% group (extreme hypercapnia) group showed increased brain damage
- Possible mechanism: increased cardiovascular depression leading to global ischemia

How important is our role?

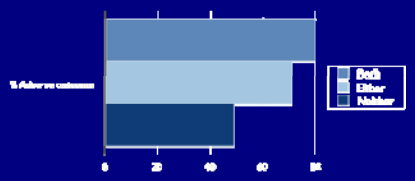
VERY!

Do hyperoxemia and hypocarbia add to the risk of brain injury after intrapartum asphyxia

- 2005 retrospective cohort study conducted at Toronto's Hospital for Sick Children
- 244 infants admitted with diagnosis of HIE - 218 with known outcomes
- Eligibility
- Five minute APGAR < 5
- Cord gas base deficit >/= 16 mmol/l
- Delayed onset of respiration for > 5 minutes
- Need for immediate mechanical ventilation
- Hyperoxemia
- Severe > 200 mmHg PaO2
- Moderate > 100 mmHg PaO2
- Hypocarbia
- Severe < 20 mmHg PaCO2
- Moderate < 25 mmHg PaCO2
- Adverse Outcomes
- Death
- Severe neurodevelopmental disability

Klinger B, Beyene J, Perlman M. Do hyperoxaemia and hypocarbia add to the risk of brain injury after intrapartum asphyxia. *Arch Dis Child Fetal Neonatal Ed* 2005;90:49-52.

Results of exposure to severe hyperoxemia and/or hypocarbia

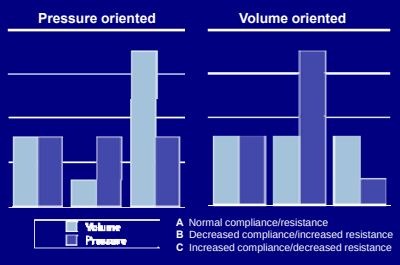


Klinger B, Beyene J, Perlman M. Do hyperoxaemia and hypocarbia add to the risk of brain injury after intrapartum asphyxia. *Arch Dis Child Fetal Neonatal Ed* 2005;90:49-52.

What can respiratory therapists do?

Neuroprotective ventilation strategies

Volume vs. Pressure



Overcoming Obstacles

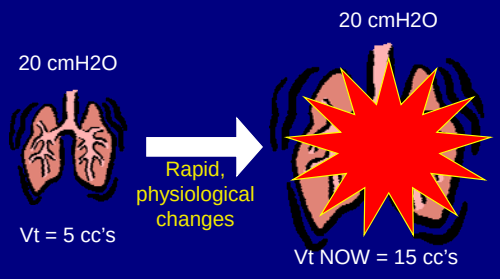
The misconception about pressure and volume

- Small animals subjected to large tidal volumes with positive and NEGATIVE pressure
- BOTH groups had evidence of lung injury REGARDLESS OF PRESSURE BEING + OR -
- Animals whose chest wall and diaphragmatic excursion were limited by external banding to MINIMIZE LARGE TIDAL VOLUMES had reduced lung injury REGARDLESS OF PRESSURE USED

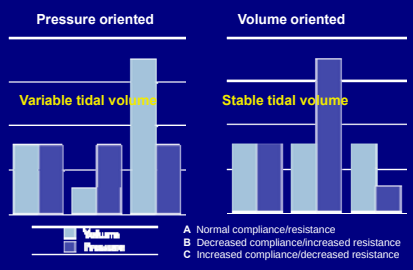
[1]**Dreyfuss D**, Saumon G. Ventilator-induced lung injury: lessons from experiemtnal studies. *Am J Respir Crit Med* 1998;**157**:294-323.

I thought pressure was bad for the lungs?

Volume is the enemy

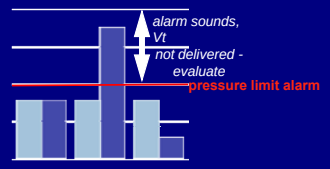


Pressure ventilation and CO2



The best of both worlds

Volume targeted/pressure limited



Volume
Pressure

A Normal compliance/resistance
B Decreased compliance/increased resistance
C Increased compliance/decreased resistance

Reducing Hypocarbia

The evidence supporting volume targeted ventilation

- Inadvertent hyperventilation ($PaCO_2$ < 25 mmHg) occurred in 30% of neonates receiving traditional pressure ventilation in randomized trial

Luyt K, Wright D. Baumer JH. Randomised study comparing extent of hypocarbia in preterm infants during conventional and patient triggered ventilation. *Arch Dis Child Detal Neonatal ED 2001*; **84**:F14-7.

- Randomized trial with 50 patients, 38 ventilated with volume guarantee (Draeger medical)
- Mean $PaCO_2$ in first 48 hours was 46.6
- $PaCO_2$ remained between 25 - 65 mmHg in 96.5% patients in the VG group

Dawson C, Davies M. Volume-targeted ventilation and arterial carbon dioxide in neonates. *J. Paediatr. Child health 2005*; **41**: 518-21.

Reducing Hypocarbia

The evidence supporting volume targeted ventilation

- Randomized trial including 40 infants: 19 assigned to VG, 21 to Pressure A/C
- Incidence of hypocarbia in infants > 25 weeks: VG - 27% vs. AC - 61%

Cheema I, Sinha A, Kempley S, Ahluwalia, J. Impact of volume guarantee ventilation on arterial carbon dioxide tensions in newborn infants: a randomised controlled trial. *Early Human Development 2007*; **83**: 183-189.

- Small study comparing $PaCO_2$ with A/C vs. A/C + VG, target $PaCO_2$ 35 - 45 mmHg
- $PaCO_2$ values < 35: AC - 36.3% vs. AC + VG - 20.1%

Keszler M, Abubakar, K. Volume guarantee: stability of tidal volume and incidence of hypocarbia. Pediatric Pulmonology *2004*; **38**: 240-45.

How does cooling impact lab values?


+

= ?

Importance of Temperature

Physiological effects of cooling

CO2

Hypothermia reduces the metabolic rate and the rate of CO_2 production. To hold the arterial CO_2 content constant during cooling it is necessary to reduce CO_2 elimination (i.e., by reducing minute ventilation in anesthetized patients) equivalently to the decrease in CO_2 production. If

Intensive Care Med (2005) 31:24–27
DOI 10.1007/s00134-004-2569-3

CO2 production can fall approximately 60% of the normal 2 to 3 mL/kg/min because hypothermia lowers metabolic activity

Lobato E, Gravenstein N, Kirby R. Complications in anesthesiology. Lippincott Williams & Wilkins 2008: 138.

O2

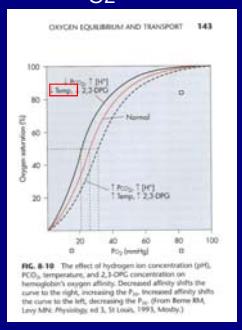


FIG. 8-10 The effect of hydrogen ion concentration (pH), PCO_2, temperature, and 2,3-DPG concentration on hemoglobin's oxygen affinity. Decreased affinity shifts the curve to the right, increasing the P_{50}. Increased affinity shifts the curve to the left, decreasing the P_{50}. (From Berne RM, Levy MN: *Physiology*, ed 3, St Louis, 1993, Mosby.)

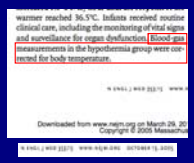
Beachey W. Respiratory care anatomy and physiology: foundations for clinical practice. Mosby 1998: 143

Temperature & ABGs

- (A-a) gradient increases with cooling
- Patient's PaO2 at actual body temperature is lower than if analyzed at 37 degrees C

- Solubility of CO2 decreases with increased temperature
- Patient's PaCO2 at actual body temperature is lower than if analyzed at 37 degrees C

Hansen D, Syben R, Vargas O, Spies C, Welte M. The alveolar-arterial difference in oxygen tension increases with temperature-corrected determination during moderate hypothermia. *Anesthesia Analg* 1998;**88**:538.


warmer reached 36.5°C. Infants received routine clinical care, including the monitoring of vital signs and surveillance for organ dysfunction. Blood-gas measurements in the hypothermia group were corrected for body temperature.

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Does cooling exacerbate PPHN ?

Cooling and PPHN

- Cooling and Pulmonary Vasculature
  - Pulmonary dysfunction is common but not severe in asphyxiated infants during therapeutic hypothermia.
- Should we hyperoxygenate?
  - In a pig model, hypoxemia induced PPHN and plasma endothelin 1 were normalized with no adverse effect when reoxygenation was performed with 21% as compared with 100% oxygen
- Hyperventilation is not indicated
  - There is very little evidence that hypocarbia reduces mortality or morbidity for patients with PPHN
- Does cooling exacerbate PPHN?
  - A question without a clear answer
    - Mild hypothermia for *24* hours in *piglets* did not affect pulmonary artery pressure pressure
    - Epidemiological evidence suggests that cooling may increase the risk of primary and/or secondary PPHN, primarily indicated by clinical situations involving an increased FiO2 requirement after initiation of cooling

Sarkar S, Barks JD, Bhagat I, Dechert R, Donn SM. Pulmonary dysfunction and therapeutic hypothermia in asphyxiated newborns: whole body versus selective head cooling. Am J Perinatol. 2009 Apr;26(4):265-70.

Fugelseth D, Borke W, Lenes K, Matthews O, Saugsta D, Thaulow E. Restoration of cardiopulmonary with 21% vs. 100% oxygen after hypoxaemia in newborn pigs. *Arch Dis Child Fetal Neonatal Ed* 2005;90:229-34.

Fugelseth D, Satas S, Steen P, Thoresen M. Cardiac output, pulmonary artery pressure, and patent ductus arteriosus during therapeutic cooling after global hypoxia-ischaemia. *Arch Dis Child Fetal Neonatal Ed* 2003;88:223-28.

Battin M, Penrice J, Gunn T, Gunn A. Treatment of term infants with head cooling and mild systemic hypothermia after perinatal asphyxia. *Pediatrics* 2003:111:224-51.

Summary

- Both hypocarbia and hyperoxemia appear to exacerbate brain injury associated with HIE and should be avoided
- Practice aggressive management of FiO2 to maintain normal PaO2 levels
- Modes of ventilation that allow for regulation of minute volume reduce the incidence of hypocarbia
- The physiologic consequences of cooling contribute to a reduction in CO2 production and oxygen consumption
- The physiologic effects of cooling must be considered when interpreting lab values
- The relationship between cooling and PPHN requires further investigation