

# Stridor in Asphyxiated Neonates Undergoing Therapeutic Hypothermia

**AUTHORS:** Judith Orme, MRCPCH, MB, ChB,<sup>a</sup> Christopher Kissack, FRCPCH, MD, FRCPE, MB, ChB, BSc (Hons),<sup>b</sup> and Julie-Clare Becher, FRCPCH, MD, FRCPE, MB, ChB<sup>b</sup>

<sup>a</sup>Department of Neonatology, Royal Infirmary of Edinburgh, United Kingdom; and <sup>b</sup>Department of Neonatology, University of Edinburgh, United Kingdom

## KEY WORDS

stridor, hypoxic-ischemic encephalopathy, treatment, side effects, hypothermia

## ABBREVIATIONS

ETT—endotracheal tube

HIE—hypoxic-ischaemic encephalopathy

Dr Orme participated in the concept and design, collected and analyzed data, and drafted the initial manuscript; Dr Kissack participated in the concept and design, designed the data collection instrument, coordinated data collection and analysis, and drafted the initial manuscript; Dr Becher conceptualized and designed the study, collected and analyzed data, and reviewed and revised the initial manuscript; and all authors approved the final manuscript as submitted.

[www.pediatrics.org/cgi/doi/10.1542/peds.2013-2053](http://www.pediatrics.org/cgi/doi/10.1542/peds.2013-2053)

doi:10.1542/peds.2013-2053

Accepted for publication Dec 26, 2013

Address correspondence to Julie-Clare Becher, FRCPCH, MD, FRCPE, MB, ChB, Department of Neonatology, Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom EH16 4SA. E-mail: [julie-clare.becher@luht.scot.nhs.uk](mailto:julie-clare.becher@luht.scot.nhs.uk)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2014 by the American Academy of Pediatrics

**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** No external funding.

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

## abstract

Therapeutic hypothermia is an established standard of care in the treatment of hypoxic-ischemic encephalopathy. Application of therapeutic hypothermia in the clinical setting may reveal a wider spectrum of adverse events than previously reported. We report 5 cases of transient respiratory stridor in 51 infants, occurring at different time points in the cooling process, which appeared to be unrelated to the intubation procedure. Therapeutic hypothermia was associated with transient stridor in this case series. Formal laryngoscopy is required to determine the underlying pathologic etiology. *Pediatrics* 2014;134:e261–e265

In resource-rich countries, therapeutic hypothermia is a standard of care in the treatment of moderate and severe neonatal hypoxic-ischemic encephalopathy (HIE).<sup>1</sup> Several meta-analyses, involving >1500 infants, have revealed no serious adverse effects of therapeutic hypothermia.<sup>2</sup> Nevertheless, professional recommendations are that treatment should occur in ICUs with sufficient expertise to manage such neurocritical infants.<sup>3,4</sup> Cooling registries of prospectively collected patient information are maintained to monitor clinical practice and to report on rare side effects that may not have been apparent in the context of clinical trials.<sup>5,6</sup>

Intubation and ventilation are commonly undertaken interventions in asphyxiated infants, but the duration of support is usually short and limited to the period of acute encephalopathy.<sup>5</sup> Cooling may increase oxygen requirements acutely but has not been otherwise reported to alter the respiratory course of asphyxiated infants.<sup>7</sup> We present a series of 5 asphyxiated infants who underwent therapeutic hypothermia, and who developed stridor during their clinical course.

## METHODS

Cases of stridor were identified from all term (>36 weeks' gestation) admis-

sions in a 4-year period from January 1, 2009, until December 31, 2012. Electronic records of infants with a diagnosis of stridor at admission, at discharge, or during hospital stay were reviewed.

## RESULTS

There were 26 413 term infants born in the study period, with an incidence of term HIE of 1.7 per 1000 live births. Fifty-one asphyxiated inborn and outborn infants underwent therapeutic hypothermia over the study period.

### Incidence of Stridor in Term Infants

Twenty-five term infants were identified with stridor either before ( $n = 19$ ) or after ( $n = 6$ ) admission to the neonatal unit, an incidence of 0.9 per 1000 live births. Of those with stridor on admission, the diagnosis was a congenital abnormality ( $n = 11$ ), vocal cord palsy ( $n = 4$ ), and a neurologic disorder ( $n = 1$ ); and in 3 infants the cause was unidentified but symptoms were transient and mild. Five cases occurred after admission in infants undergoing therapeutic hypothermia, 9.6% of all cooled infants; each is described below (Table 1). Only 1 nonasphyxiated term infant had transient stridor reported after an intubation period of 20 minutes.

## Cooling and Intubation Protocols

The local cooling protocol is based on standard recommendations for the treatment of asphyxiated newborns.<sup>8,9</sup> Whole-body hypothermia is induced and maintained by using the CritiCool Cooling System (Charter Kontron, Milton Keynes, United Kingdom). Sedation of infants with morphine is standard practice. Endotracheal intubation is performed when clinically indicated, and infants may be extubated during therapeutic hypothermia if status allows. Junior staff are encouraged to attempt 2 intubations under senior supervision. The use of a stylet introducer is not routine and is discouraged. An uncuffed, nonshouldered endotracheal tube (ETT) is used, and placement is confirmed with a carbon dioxide colorimeter, auscultation, and chest radiograph. Endotracheal suction is performed when clinically indicated, although not routinely. Inspired ventilator gases are humidified and heated to 37°C.

### Cases of Stridor in Infants Undergoing Therapeutic Hypothermia

Five infants (1 boy, 4 girls) were born between 39 and 41 weeks' gestation, with birth weights from 2770 to 4240 g. All infants suffered intrapartum asphyxia, and arterial cord pH values

**TABLE 1** Clinical Details of Stridor Cases

Case Number	Birth Weight, g	Age at Intubation (Number of Attempts), ETT Size	Age at Extubation, h	Age at Onset of Stridor, h (Relationship to Cooling Process)	Core Temperature, °C	Treatment Received for Stridor	Duration of Stridor, h	Other Organ Injury (Max Values)
1	3755	4 min (3), 3.5 mm	10	89 (rewarming)	36.5	Intubation IPPV, surfactant	11	Creatinine: 128 μM/L; ALT: 190 IU/L
2	2770	Never	NA	84 (rewarming)	35.1	NPA, antibiotics	24	Creatinine: 108 μM/L; ALT: 44 IU/L
3	4240	7 min (2), 3.5 mm	55	59 (active cooling)	33.5	Prone position	24	Creatinine: 75 μM/L; ALT: 148 IU/L
4	3325	7 min (1), 3.5 mm; 16 h (2), 4 mm	121	121 (36-h after rewarming)	36.8	CPAP, dexamethasone, adrenaline	34	Creatinine: 145 μM/L; ALT: 367 IU/L
5	3135	6 min (2), 3.5 mm	6	92 (8-h after rewarming)	36.7	CPAP	9	Creatinine: 80 μM/L; ALT: 16 IU/L

ALT, alanine aminotransferase; CPAP, continuous positive airway pressure; IPPV, intermittent positive pressure ventilation; Max, maximum; NA, not applicable; NPA, nasopharyngeal airway.

ranged from 6.86 to 6.89. No infant experienced dystocia or showed signs of peripheral nerve paralysis during admission. All infants developed moderate/severe HIE and underwent therapeutic hypothermia. There was evidence of mild renal and hepatic involvement in 3 infants (Table 1).

At the time of stridor, serum calcium and magnesium levels were normal in 3 infants, 1 infant had an ionized calcium level of 0.88 mmol/L, and another had a magnesium level of 0.69 mmol/L. Serum sodium ranged from 125 to 134 mmol/L, and the urine output range was 1.1 to 5.1 mL/kg per hour at the time of stridor, reflecting the variation in output seen in acute renal injury and recovery. No infant showed interstitial edema other than that occurring normally during the cooling process; there was also no evidence of significant fluid overload. In only 1 infant (case 1), the larynx was inspected at reintubation when there was no report of obvious airway abnormality.

#### Case 1

At birth, meconium was suctioned from this infant's trachea. Intubation was successful on the third attempt with an introducer and a size 3.5 ETT at 4 minutes. The infant was extubated at 10 hours into air with good respiratory drive.

Twelve hours into rewarming, with a core temperature of 36.5°C, marked respiratory distress was observed with an obstructive breathing pattern and respiratory acidosis ( $P_{CO_2}$  of 10.3 kPa). Uneventful reintubation under direct laryngoscopy relieved the work of breathing, and despite minimal oxygen requirement, surfactant was administered because of suspected hypothermia-induced surfactant deficiency. The infant was not receiving morphine or anti-convulsants and was extubated to air 11 hours later with no further respiratory difficulty.

#### Case 2

At birth, the infant received mask ventilation and cardiac compressions. Regular respiratory effort was established at 12 minutes. From 1 hour of age the infant was nursed in air and was never ventilated, nor was intubation or endotracheal suction ever attempted.

Four hours into rewarming, with a core temperature of 35.1°C, acute stridor was noted with tracheal tug and desaturation ( $P_{CO_2}$  of 8.5 kPa). Airway obstruction was ameliorated with a nasopharyngeal airway. A morphine infusion was reduced and rewarming slowed to 0.2°C per hour. Antibiotics were commenced for possible bacterial tracheitis, but infection markers and cultures proved negative. The stridor resolved within 48 hours.

#### Case 3

At birth, the infant received mask ventilation and chest compressions. Intubation occurred at 7 minutes with a size 3.5 ETT by the senior doctor after 1 attempt by the junior doctor. One dose of phenobarbitone was administered for seizures at 13 hours.

At 55 hours of age, with a core temperature of 33.5°C, the infant was extubated to air while receiving morphine. Mild biphasic stridor was noted 4 hours later but was not associated with increased work of breathing nor did it require any intervention ( $P_{CO_2}$  of 5.9 kPa). Stridor was evident for a further 24 hours, and the subsequent rewarming period was uncomplicated.

#### Case 4

At birth, the infant received mask ventilation and cardiac compressions. Intubation occurred on the first attempt at 7 minutes with a size 3.5 ETT. On day 1, there was an accidental extubation and reintubation occurred on the second attempt with a size 4 ETT. Two doses of phenobarbitone were administered for seizures.

On day 6 of life, 36 hours after reaching normothermia, extubation occurred. There was immediate stridor, increased work of breathing, desaturation, and the  $P_{CO_2}$  increased to 7.1 kPa. Symptoms were relieved with nebulized adrenaline, intravenous dexamethasone, and continuous positive airway pressure; and intermittent mild stridor was audible for an additional 30 hours.

#### Case 5

At birth, suction was performed under direct vision. Intubation occurred on the second attempt at 7 minutes with a size 3.5 ETT. The infant was extubated at 6 hours of age and remained breathing in air through treatment with phenobarbitone and phenytoin for seizures at 14 hours of age. Rewarming followed uneventfully at 72 hours of age.

Seven hours after reaching normothermia, there was desaturation and increased work of breathing with biphasic stridor ( $P_{CO_2}$  of 8.3 kPa). The infant was nursed prone and placed on continuous positive airway pressure for 24 hours until stridor had resolved.

## DISCUSSION

As widespread implementation of therapeutic hypothermia occurs, regional guidelines and pathways have been increasingly established and early concerns about the safety of therapeutic hypothermia are subsiding as a body of experience accrues within the neonatal community.

However, although randomized trials and meta-analyses reassure that significant side effects of cooling are few and mild, they are not powered to detect rare events that may become apparent when therapeutic hypothermia is implemented on a wider scale and within routine practice. In addition, rarely is the scope of randomized trials such that all possible adverse events are sought or evaluated.

National registers encourage reporting of individual cases to audit practice and outcomes but also to inform on the rare side effects of cooling.<sup>5,6</sup> Of relevance is the evidence that subcutaneous fat necrosis and lidocaine-induced arrhythmias may be more common in infants who undergo therapeutic hypothermia.<sup>5,10</sup>

We report on 5 infants who underwent therapeutic hypothermia for intrapartum asphyxia and who developed stridor during admission. Stridor was not necessarily related to tracheal intubation, difficulty in intubation, or the duration of ventilation. Intubation practice did not change during the study period nor was stridor observed in noncooled, ventilated infants, suggesting that this phenomenon was not related to the procedure of intubation alone. Moreover, stridor was not temporally related to extubation and occurred as remotely as 71 hours after ETT removal. A limitation of this series is that formal laryngeal examination was undertaken in only 1 case, but the temporary nature of the obstruction implies a functional rather than a structural etiology. Nevertheless, direct laryngoscopy is essential in determining pathologic etiology and is planned in future cases.

Stridor occurred during all phases of hypothermia treatment, including during active cooling, rewarming, and normothermia. In all cases, the stridor was transient and resolved within 48 hours. All infants demonstrated good respiratory drive, and the absence of encephalopathy or sedation at the time of stridor in some cases implies that neurologic depression or injury is un-

likely to have contributed to the acute airway obstruction observed.

It is well recognized that glottal mechanics are sensitive to changes in core temperature, such that increases in temperature result in an increase in the force of the glottal closing reflex and vice versa.<sup>11</sup> In animals, the glottal closing force increases 300% to 400% over a similar temperature range as occurs during rewarming,<sup>12</sup> and it may follow that temperature fluctuations experienced during servo-controlled cooling result in alteration of glottal mechanics. Alternatively, the increase in the extracellular fluid compartment secondary to capillary leak that occurs during cooling<sup>13</sup> has the potential to result in edema of the upper airway and an increase in resistance, which resolves as this compartment contracts.

No cases of respiratory stridor have been reported to the UK TOBY Cooling Register or the Vermont Oxford Network (VON) Neonatal Encephalopathy Registry (D. Azzopardi, FRCHPCH and B. Strohm, RN on behalf of the UK TOBY Cooling Register, personal communication, 2013; R. Pfister, MD on behalf of the VON Neonatal Encephalopathy Registry, personal communication, 2013), although the authors are aware of 2 infants in 2 other UK institutions who developed stridor during therapeutic hypothermia. We assume that occasional instances may not be regarded as an association of therapeutic hypothermia per se but as a complication of intubation, and therefore the problem may be underreported. In addition, almost half of all centers providing data to the TOBY register reported that they treat  $\leq 6$  infants

per year, and as such, infrequent adverse effects may not have been experienced (D. Azzopardi and B. Strohm on behalf of the UK TOBY Cooling Register, personal communication, 2013).

Although not described as a significant adverse effect of cooling in meta-analyses, a multicenter safety pilot trial reported the occurrence of stridor in 9 of 31 cooled infants compared with 1 of 33 control infants ( $P < .01$ ), an incidence of 29%.<sup>14</sup> These infants responded to nebulized adrenaline, and the authors hypothesized that the stridor was related to transient tracheal swelling after ventilation with humidified air of 34°C. In our center, inspired gases are warmed and humidified to 37°C.

Therapeutic hypothermia has been shown to improve outcome in adults after out-of-hospital cardiac arrest; stridor or airway obstruction is not reported as an adverse effect.<sup>15,16</sup> Published cohort studies in pediatric patients undergoing hypothermia after cardiac arrest do not list stridor as an adverse effect,<sup>17,18</sup> but the outcomes of a large randomized controlled trial in this population have yet to be published (F. Moler, MD, MS, FCCM on behalf of the Therapeutic Hypothermia after Pediatric Cardiac Arrest- Out of Hospital (THAPCA-OH) trial, personal communication, 2013).

In our case series, stridor was associated with hypothermia treatment in hypoxic-ischemic encephalopathy, but not with severe compromise. In all infants, symptoms resolved within 48 hours. The neuroprotective benefit of therapeutic hypothermia outweighs this small risk of transient stridor.

## REFERENCES

1. Edwards AD, Brocklehurst P, Gunn AJ, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *BMJ*. 2010;340(Feb 9):c363
2. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Rev*. 2013 (Jan 31)
3. National Institute for Health and Clinical Excellence. IPG347: therapeutic hypothermia

- with intracorporeal temperature monitoring for hypoxic perinatal brain injury. NICE Interventional Procedure Guidance, May 2010. Manchester, United Kingdom: National Institute for Health and Clinical Excellence; 2010
4. Adams E, Austin T, Becher JC, et al; British Association of Perinatal Medicine. Position statement on therapeutic cooling for neonatal encephalopathy. BAPM 2010
  5. Azzopardi D, Strohm B, Linsell L, et al; UK TOBY Cooling Register. Implementation and conduct of therapeutic hypothermia for perinatal asphyxial encephalopathy in the UK—analysis of national data. *PLoS ONE*. 2012;7(6):e38504
  6. Pfister RH, Bingham P, Edwards EM, et al. The Vermont Oxford Neonatal Encephalopathy Registry: rationale, methods, and initial results. *BMC Pediatr*. 2012;12:84
  7. Thoresen M, Whitelaw A. Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. *Pediatrics*. 2000;106(1 pt 1):92–99
  8. Thoresen M. Hypothermia after perinatal asphyxia: selection for treatment and cooling protocol. *J Pediatr*. 2011;158(2 suppl):e45–e49
  9. National Perinatal Epidemiology Unit. The UK TOBY Cooling Register. Available at: [www.npeu.ox.ac.uk/tobyregister](http://www.npeu.ox.ac.uk/tobyregister). Accessed November 1, 2013
  10. Strohm B, Hobson A, Brocklehurst P, Edwards AD, Azzopardi D; UK TOBY Cooling Register. Subcutaneous fat necrosis after moderate therapeutic hypothermia in neonates. *Pediatrics*. 2011;128(2):e450–e452
  11. Wadie M, Li J, Sasaki CT. Effect of altered core body temperature on glottal closing force. *Ann Otol Rhinol Laryngol*. 2011;120(10):669–673
  12. Harağuchi S, Fung RQ, Sasaki CT. Effect of hyperthermia on the laryngeal closure reflex: implications in the sudden infant death syndrome. *Ann Otol Rhinol Laryngol*. 1983;92(1 pt 1):24–28
  13. Hammersborg SM, Farstad M, Haugen O, Kvalheim V, Onarheim H, Husby P. Time course variations of haemodynamics, plasma volume and microvascular fluid exchange following surface cooling: an experimental approach to accidental hypothermia. *Resuscitation*. 2005;65(2):211–219
  14. Eicher DJ, Wagner CL, Katikaneni LP, et al. Moderate hypothermia in neonatal encephalopathy: safety outcomes. *Pediatr Neurol*. 2005;32(1):18–24
  15. Nolan JP, Morley PT, Vanden Hoek TL, et al; International Liaison Committee on Resuscitation. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation*. 2003;108(1):118–121
  16. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med*. 2009;37(3):1101–1120
  17. Fink EL, Clark RS, Kochanek PM, Bell MJ, Watson RS. A tertiary care center's experience with therapeutic hypothermia after pediatric cardiac arrest. *Pediatr Crit Care Med*. 2010;11(1):66–74
  18. Moler FW, Donaldson AE, Meert K, et al; Pediatric Emergency Care Applied Research Network. Multicenter cohort study of out-of-hospital pediatric cardiac arrest. *Crit Care Med*. 2011;39(1):141–149

## Stridor in Asphyxiated Neonates Undergoing Therapeutic Hypothermia

Judith Orme, Christopher Kissack and Julie-Clare Becher

*Pediatrics* 2014;134:e261

DOI: 10.1542/peds.2013-2053 originally published online June 9, 2014;

### Updated Information & Services

including high resolution figures, can be found at:  
<http://pediatrics.aappublications.org/content/134/1/e261>

### References

This article cites 14 articles, 3 of which you can access for free at:  
<http://pediatrics.aappublications.org/content/134/1/e261#BIBL>

### Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
<http://www.aappublications.org/site/misc/Permissions.xhtml>

### Reprints

Information about ordering reprints can be found online:  
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## **Stridor in Asphyxiated Neonates Undergoing Therapeutic Hypothermia**

Judith Orme, Christopher Kissack and Julie-Clare Becher

*Pediatrics* 2014;134:e261

DOI: 10.1542/peds.2013-2053 originally published online June 9, 2014;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/134/1/e261>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2014 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

