

Results | The LTL (expressed in the telomere repeat copy number to the single gene copy number ratio) remained unchanged during and after the OC intake. In contrast, the LTL doubled while taking PioFluMet and returned to baseline after the PioFluMet intake was stopped (Figure). The LTL changes across treatment groups during 18 months related inversely to fasting insulinemia, body fat fraction by dual energy x-ray absorptiometry, and visceral and hepatic adiposity by magnetic resonance imaging (all r values were between -0.53 and -0.57 ; all P values were between 0.002 and 0.007). The ratio of circulating neutrophils to lymphocytes was first similar in treatment groups and remained similar in and between groups across 24 months. Noteworthy adverse effects were not encountered in either treatment group.⁴

Discussion | Prolonged insulin sensitization (with PioFluMet) is emerging as a first approach with antiaging effects and includes a slow marked reversible increment of LTL in adolescent girls with HIAE.

A comparably marked LTL increment was reported on initiating the treatment with sitagliptin in older Chinese adults with type 2 diabetes mellitus.⁵ In that study, telomere lengths were in the subnormal range at the start of treatment and increased to a healthy range within 2 months in parallel with improved glucose level control. In our young study population, telomere lengths were in the healthy range at the start of treatment and increased to the supranormal range after a longer intervention (12 to 18 months) in the absence of diabetes mellitus.

Future studies should disclose whether other insulin-sensitizing interventions (such as flutamide being replaced by spironolactone) can also elicit telomere lengthening in late adolescence and whether telomerase activity is up-regulated, either indirectly by a less adipose and more insulin-sensitive state or directly by components, such as pioglitazone, that can up-regulate the transcription of telomerase reverse transcriptase.⁶ Nevertheless, we may be closer to understanding why some insulin-sensitive women stay forever young.

Francis de Zegher, MD, PhD

Marta Díaz, PhD

Lourdes Ibáñez, MD, PhD

Author Affiliations: Department of Development and Regeneration, University of Leuven, Leuven, Belgium (de Zegher); Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Spain (Díaz, Ibáñez); Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Madrid, Spain (Díaz, Ibáñez).

Corresponding Author: Francis de Zegher, MD, PhD, Department of Development and Regeneration, University of Leuven, Herestraat 49, 3000 Leuven, Belgium (francis.dezegher@uzleuven.be).

Published Online: June 15, 2015. doi:10.1001/jamapediatrics.2015.0439.

Author Contributions: Dr de Zegher had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: de Zegher, Díaz.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: de Zegher.

Critical revision of the manuscript for important intellectual content: Díaz, Ibáñez.

Administrative, technical, or material support: Díaz.

Study supervision: All authors.

Conflict of Interest Disclosures: None reported.

- Benetos A, Kark JD, Susser E, et al. Tracking and fixed ranking of leukocyte telomere length across the adult life course. *Aging Cell*. 2013;12(4):615-621.
- Ibáñez L, Ong KK, López-Bermejo A, Dunger DB, de Zegher F. Hyperinsulinaemic androgen excess in adolescent girls. *Nat Rev Endocrinol*. 2014;10(8):499-508.
- Legro RS, Arslanian SA, Ehrmann DA, et al; Endocrine Society. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2013;98(12):4565-4592.
- Ibáñez L, Díaz M, Sebastiani G, Marcos MV, López-Bermejo A, de Zegher F. Oral contraception vs insulin sensitization for 18 months in nonobese adolescents with androgen excess: posttreatment differences in C-reactive protein, intima-media thickness, visceral adiposity, insulin sensitivity, and menstrual regularity. *J Clin Endocrinol Metab*. 2013;98(5):E902-E907.
- Ma D, Yu Y, Yu X, Zhang M, Yang Y. The changes of leukocyte telomere length and telomerase activity after sitagliptin intervention in newly diagnosed type 2 diabetes. *Diabetes Metab Res Rev*. 2015;31(3):256-261.
- Spyridopoulos I. Is telomerase a potential target for vascular rejuvenation? *Atherosclerosis*. 2011;216(1):19-20.

A Living Systematic Review of Nebulized Hypertonic Saline for Acute Bronchiolitis in Infants

Grewal and Klassen¹ in *JAMA Pediatrics* note the frustrations in interpreting evidence about bronchiolitis. Evidence is spread across a prior meta-analysis and other trials. The Grewal and Klassen editorial¹ encourages living systematic reviews that are updated as new trials emerge. We use the topic of nebulized hypertonic saline for bronchiolitis to propose the method of a living systematic review.

Methods | In this meta-analysis, we started by including the same trials in the Cochrane review by Zhang et al.² We then searched for newer trials in the Cochrane Central Register of Controlled Trials and articles in Web of Science that cited the Zhang et al study.² Our methods are detailed online at the living review (<http://openmetaanalysis.github.io/Hypertonic-Saline-for-Bronchiolitis/>).

Results | We identified 11 new trials (4 only available at <http://clinicaltrials.gov>).¹ The meta-analysis showed that hypertonic saline significantly reduced the length of stay (LOS) among hospitalized infants. Heterogeneity was largely owing to variation in LOS in the control groups of trials. Benefit was confined to studies with a long LOS; however, even within this group study, results of recent trials were negative. Among infants given multiple doses, symptoms were improved and hospitalization was reduced. Forest plots, meta-regressions, and risk of bias assessment are available online. Quality of evidence as assessed by the GRADEprofiler was low owing to imprecision and other factors detailed in the GRADEprofiler online.

Discussion | Prior research was comprehensively summarized by the Cochrane review. The addition of the newer trials attenuated the results of all outcomes. However, all outcomes were statistically significant owing to reduction in hospitalization in the subgroup analysis of infants who received multiple doses of treatment. The reduction in LOS was confined to older trials with a longer LOS. We rated the quality of evidence lower than the Cochrane review. This is likely owing to

Box. Living Systematic Review Opportunities

Knowledge Creation

Living reviews may accompany requests for funding or ethics approval to justify proposed research.

Living reviews may accompany manuscripts during peer review to place research in context.

Living reviews can be done by nontrialists when a trial that is not accompanied by a systematic review is published and affects a body of evidence.

Living reviews may encourage collaboration by reducing barriers to contributions by individuals.

Medical Education

Living reviews or updates to reviews that consist of a few trials may be authored by supervised trainees.

Living reviews may help teach numeracy by assessing the change in outcomes and heterogeneity after adding new studies.

Living reviews may teach epistemological concepts if the methods of GRADE and QUADAS-2 are used.

Living reviews may provide up-to-date content for tertiary educational publications, such as wikis. This is supported by GNU General Public Licensing.

downgrading evidence according to criteria listed in our summary of findings table and methods (<http://openmetaanalysis.github.io/Hypertonic-Saline-for-Bronchiolitis/>). The small number of patients studied limit both generalizability and the certainty of conclusions.

This topic validates the Grewal and Klassen¹ recommendation for living systematic reviews. Further, a practice guideline³ and meta-analysis⁴ on the same topic were published this year and neither included the newer trials. Living reviews provide opportunities (Box) to advance knowledge creation, discourage unnecessary trials, and prevent under-recognition of prior research by trialists⁵ and authors.⁶ In addition, living reviews may help medical education via experiential learning (Box).

Repositories of living systematic reviews may be hosted at GitHub (<http://openmetaanalysis.github.io/>), as we did, or at the Systematic Review Data Repository (<http://srd.ahrq.gov/>). GitHub provides web hosting and sharing repositories with version control. In addition, it offers wikis, issue tracking, communication, and social networking features that facilitate rapid collaborative knowledge work. Beyond sharing code, GitHub now hosts projects ranging from simple documents to complex governmental legislation.

Methods for living systematic reviews will evolve both technically and procedurally. For example, should open repositories include exhaustive interpretations of data? We propose that repositories should focus on the data and then link to interpretations of data in journals or tertiary publications, such as online textbooks and wikis. How can living reviews be designed to complement rather than compete with exhaustive reviews published by Cochrane and others? One solution is that when the published review is current, the living review will indicate there are no recent trials and link to the exhaustive review.

Available evidence, although low quality, suggests that hypertonic saline for bronchiolitis decreases the LOS for hospitalized children and may reduce symptoms and the rate of hospitalization. We encourage colleagues to help maintain this review, create other reviews, and advance the methods of living systematic reviews. Analyses and figures will be updated at <http://openmetaanalysis.github.io/Hypertonic-Saline-for-Bronchiolitis/> as new trials are published.

Robert G. Badgett, MD
Mohinder Vindhyal, MD
Jason T. Stirnaman, MLS
C. Michael Gibson, MD
Rim Halaby, MD

Author Affiliations: Department of Internal Medicine, Kansas University School of Medicine, Wichita (Badgett, Vindhyal); Department of Preventive Medicine and Public Health, Kansas University School of Medicine, Wichita (Badgett); Department of Pediatrics, Kansas University School of Medicine, Wichita (Vindhyal); A. R. Dykes Library, Kansas University School of Medicine, Wichita (Stirnaman); PERFUSE Study Group, Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts (Gibson, Halaby).

Corresponding Author: Robert G. Badgett, MD, Departments of Internal Medicine, Preventive Medicine, and Public Health, Kansas University School of Medicine, 1010 N Kansas St, Wichita, KS 67214-3199 (rbadgett@kumc.edu).

Published Online: June 22, 2015. doi:10.1001/jamapediatrics.2015.0681.

Author Contributions: Dr Badgett had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Badgett, Stirnaman.

Acquisition, analysis, or interpretation of data: Badgett, Vindhyal, Gibson, Halaby.

Drafting of the manuscript: Badgett, Vindhyal, Stirnaman.

Critical revision of the manuscript for important intellectual content: Badgett, Stirnaman, Gibson, Halaby.

Statistical analysis: Badgett, Vindhyal, Gibson.

Administrative, technical, or material support: Badgett, Vindhyal, Stirnaman.

Study supervision: Badgett.

Conflict of Interest Disclosures: None reported.

Additional Contributions: We acknowledge the patient assistance provided directly and indirectly by Jeroen Ooms, PhD, Department of Statistics, University of California Los Angeles, creator of <https://www.opencpu.org/>, and Guido Schwarzer, PhD, Institute for Medical Biometry and Statistics, Medical Center; University of Freiburg, Germany, author of <http://cran.r-project.org/web/packages/meta/>. Neither individual received financial compensation.

1. Grewal S, Klassen TP. The tale of 2 trials: disentangling contradictory evidence on hypertonic saline for acute bronchiolitis. *JAMA Pediatr*. 2014;168(7):607-609.

2. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev*. 2013;7:CD006458.

3. Ralston SL, Lieberthal AS, Meissner HC, et al; American Academy of Pediatrics. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134(5):e1474-e1502.

4. Chen YJ, Lee WL, Wang CM, Chou HH. Nebulized hypertonic saline treatment reduces both rate and duration of hospitalization for acute bronchiolitis in infants: an updated meta-analysis. *Pediatr Neonatol*. 2014;55(6):431-438.

5. Cooper NJ, Jones DR, Sutton AJ. The use of systematic reviews when designing studies. *Clin Trials*. 2005;2(3):260-264.

6. Robinson KA, Goodman SN. A systematic examination of the citation of prior research in reports of randomized, controlled trials. *Ann Intern Med*. 2011;154(1):50-55.