

lytic magnesium sulfate before randomization. This is problematic, since women who were exposed both before and after randomization had a higher rate of infant death (10.9%) than did women who did not receive such therapy before randomization (9.2%), although the difference between the two groups was not significant. The median prophylactic dose in the study by Rouse et al. was 31.5 g. However, the higher doses among women given magnesium sulfate for tocolysis before randomization were not reported.

With respect to the use of magnesium sulfate for neuroprophylaxis, the study by Rouse et al. is indeterminate. Likewise, the accompanying editorial by Stanley and Crowther<sup>5</sup> does not recommend its use. With all things considered, we remain gravely concerned about potential harm from high-dose magnesium sulfate in preterm labor.

Robert Mittendorf, M.D., Dr.P.H.

Loyola University Medical Center  
Maywood, IL 60153  
rmitten@lumc.edu

Peter G. Pryde, M.D.

University of Wisconsin Medical School  
Madison, WI 53703

1. Rouse DJ, Hirtz DG, Thom E, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med* 2008;359:895-905.
2. Mittendorf R, Covert R, Boman J, Khoshnood B, Lee KS, Siegler M. Is tocolytic magnesium sulphate associated with increased total paediatric mortality? *Lancet* 1997;350:1517-8.
3. Mittendorf R, Roizen N, Siegler M, Khoshnood B, Lee K-S. Tocolytic magnesium sulphate and paediatric mortality. *Lancet* 1998;351:293.
4. Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev* 2002;4:CD001060.
5. Stanley EJ, Crowther C. Antenatal magnesium sulfate for neuroprotection before preterm birth? *N Engl J Med* 2008;359:962-4.

**THE AUTHORS REPLY:** We can allay the concerns of Mittendorf and Pryde. In our study, neither the total dose of magnesium sulfate that was administered nor the concentration of magnesium in

umbilical cord blood at birth was associated with stillbirth or infant death. For example, in unpublished analyses that excluded infants with major congenital malformations and were adjusted for maternal race, gestational age at delivery, and the presence or absence of chorioamnionitis, the odds ratio for death in the quartile receiving the highest total dose (range, 44 to 201 g) was 1.01 (95% CI, 0.48 to 2.10). Similarly, the respective odds ratio for the quartile with the highest level of cord-blood magnesium at birth (3.4 to 5.4 meq per liter) relative to the lowest quartile (<0.4 to 1.7 meq per liter) was 0.82 (95% CI, 0.36 to 1.84). As to whether our results were indeterminate, although magnesium sulfate had no significant effect on the rate of infant death, it significantly lowered the rate of mild, moderate, and severe cerebral palsy, findings that are consistent with the two other large and well-done trials of magnesium sulfate for fetal neuroprotection.<sup>1,2</sup>

Dwight J. Rouse, M.D.

University of Alabama at Birmingham  
Birmingham, AL 35249  
drouse@uab.edu

Deborah G. Hirtz, M.D.

National Institute of Neurological Disorders and Stroke  
Bethesda, MD 20892

Elizabeth A. Thom, Ph.D.

George Washington University Biostatistics Center  
Rockville, MD 20852

for the Eunice Shriver Kennedy National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network

1. Crowther CA, Hiller JE, Doyle LW, Haslam RR. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. *JAMA* 2003;290:2669-76.
2. Marret S, Marpeau L, Follet-Bouhamed C, et al. Effect of magnesium sulphate on mortality and neurologic morbidity of the very-preterm newborn (of less than 33 weeks) with two-year neurological outcome: results of the prospective PREMAG trial. *Gynecol Obstet Fertil* 2008;36:278-88. (In French.)

## Continuous Glucose Monitoring and Type 1 Diabetes

**TO THE EDITOR:** The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group (Oct. 2 issue)<sup>1</sup> concluded that “continuous glucose monitoring can be associated with improved glycemic control in adults with type 1 diabetes.” The authors assessed continuous glucose monitoring using three different devices (DexCom

Seven, MiniMed Paradigm Real-Time Insulin Pump and Continuous Glucose Monitoring System, and FreeStyle Navigator). The evaluation of accuracy, performance, and reproducibility of different continuous-glucose-sensor systems is not straightforward, especially if taken in the context of established accuracy measures such as correlation

or regression.<sup>2</sup> It has been reported that the sensitivity of FreeStyle Navigator and MiniMed might vary and that further refinements in technology might be required before every system could be used for clinical purposes.<sup>3</sup> Moreover, Kovatchev et al. found that the numerical errors of the Dex-Com device as compared with other tree devices were approximately 30% larger.<sup>4</sup> The different analytic performances of the different continuous-glucose-sensor devices makes standardizing and harmonizing their measurements challenging. Thus, the potential problems stemming from the use of different continuous-glucose-monitoring systems should be acknowledged in evaluating results of multicenter clinical trials.

Martina Montagnana, M.D.

Giuseppe Lippi, M.D.

Gian Cesare Guidi, M.D.

University of Verona  
37134 Verona, Italy  
martina.montagnana@med.lu.se

1. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008; 359:1464-76.
2. Parkes JL, Slatin SL, Pardo S, Ginsberg BH. A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. *Diabetes Care* 2000;23: 1143-8.
3. Clarke WL, Anderson S, Farhy L, et al. Evaluating the clinical accuracy of two continuous glucose sensors using continuous glucose-error grid analysis. *Diabetes Care* 2005;28:2412-7.
4. Kovatchev B, Anderson S, Heinemann L, Clarke W. Comparison of the numerical and clinical accuracy of four continuous glucose monitors. *Diabetes Care* 2008;31:1160-4.

**TO THE EDITOR:** The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group provides convincing evidence to support continuous glucose monitoring as a means of reducing glycated hemoglobin. The use of absolute and derivative functions from continuous glucose monitoring may also help limit the risk of hypoglycemia. The authors report rates of self-reported hypoglycemia that are similar to those in previous studies.<sup>1</sup> However, their measure of mean time per day at a blood glucose level of 70 mg per deciliter (3.9 mmol per liter) or lower does not appear to have any clinical correlate. To exploit continuous monitoring in the management of hypoglycemia and capture episodes in patients with hypoglycemia unawareness, a consensus is required on what constitutes a hypoglycemic event in real time. The U.K. Hypoglycaemia Study Group defined a hypoglycemic event as 20 minutes or more with a blood glucose level of less

than 54 mg per deciliter (3.0 mmol per liter).<sup>2</sup> This compound measure reflects the duration and blood glucose level at which cognitive function deteriorates in physiological studies.<sup>3,4</sup> Re-analysis of the data with a similar definition of biochemical hypoglycemia or further study of a more selected population is warranted to evaluate whether real-time monitoring offers any benefit in preventing hypoglycemia.

Alexander E.T. Finlayson, M.B., B.S., B.Med.Sci.

King's College Hospital  
London SE5 9RS, United Kingdom  
alexanderfinlayson@gmail.com

Nathalie J. Cronin, M.B., B.S., B.Sc.

Jersey General Hospital  
St Helier JE1 3QS, United Kingdom

Pratik Choudhary, M.B., B.S.

King's College Hospital  
London SE5 9RS, United Kingdom

Dr. Choudhary reports receiving an honorarium from Medtronic. No other potential conflict of interest relevant to this letter was reported.

1. Donnelly LA, Morris AD, Frier BM, et al. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. *Diabet Med* 2005;22:749-55.
2. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007;50:1140-7.
3. Deary IJ. Effects of hypoglycaemia on cognitive function. In: Frier BM, Fisher BM, eds. *Hypoglycaemia and diabetes: clinical and physiological aspects*. London: Edward Arnold, 1993:80-92.
4. Evans ML, Pernet A, Lomas J, Jones J, Amiel SA. Delay in onset of awareness of acute hypoglycemia and of restoration of cognitive performance during recovery. *Diabetes Care* 2000;23: 893-7.

**THE AUTHORS REPLY:** In response to Montagnana et al.: our trial was not a study to evaluate the accuracy of continuous glucose monitoring or to compare outcomes according to a specific device, but rather it was a clinical trial to evaluate the effectiveness of this technology when incorporated into daily diabetes management. Although future generations of continuous-glucose-monitoring devices are likely to have greater accuracy, we believe that the accuracy of the continuous-glucose-monitoring systems that are currently available commercially is sufficient for the devices to be beneficial. Our trial results support this. We found that most adults in the continuous-monitoring group used the device on a daily or near-daily basis for the duration of the trial and had a substantial decrease in the mean glycated hemoglobin level, as compared with the control group ( $P < 0.001$ ), without an increase in hypoglycemia. Children and adolescents in the continu-

ous-monitoring group were less likely to use the continuous-glucose-monitoring device regularly, but those who did had a reduction in the glycated hemoglobin level that was of similar magnitude to the reduction seen in the adults (among subjects in the continuous-monitoring group, who averaged 6.0 or more days per week of continuous-glucose-monitor use over the 26-week period of the study, the mean decrease in the glycated hemoglobin level from baseline to 26 weeks was 0.5% in subjects  $\geq 25$  years old, 0.5% in those 15 to 24 years old, and 0.7% in those 8 to 14 years old).

In response to Finlayson et al.: the hypoglycemia event rate ( $\geq 20$  minutes with a glucose level of  $< 54$  mg per deciliter), with combined data for the week after the 13-week visit and the week after the 26-week visit, was 0.25 event per 24 hours in the continuous-monitoring group and 0.33 event per 24 hours in the control group

( $P=0.03$ ). Treatment-group differences in event rates ranged from 0.08 to 0.10 in the three age groups. These data provide further support for the ability of continuous glucose monitoring to reduce glycated hemoglobin levels in adults without increasing hypoglycemia.

William V. Tamborlane, M.D.

Yale University  
New Haven, CT 06520

Roy W. Beck, M.D., Ph.D.

Jaeb Center for Health Research  
Tampa, FL 33647  
rbeck@jaeb.org

Lori Laffel, M.D., M.P.H.

Joslin Diabetes Center  
Boston, MA 02215

for the Juvenile Diabetes Research Foundation  
Continuous Glucose Monitoring Study Group

## Monoclonal Antibody Therapy and Non-Hodgkin's Lymphoma

**TO THE EDITOR:** In their review of monoclonal antibody therapy for B-cell non-Hodgkin's lymphoma (Aug. 7 issue),<sup>1</sup> Cheson and Leonard did not mention a potential cause of resistance to this treatment. Statins, by depleting cholesterol in the cell membrane, have been shown to diminish the antitumor effects of rituximab in vitro (as well as in a small exploratory study in vivo) by inducing conformational changes in CD20, resulting in reduced anti-CD20 binding.<sup>2</sup> It is plausible that statins also induce changes in other surface antigens and likewise reduce the antitumor effects of other monoclonal antibodies. Physicians should be aware of this form of resistance, and suspend statin therapy during monoclonal antibody treatment of non-Hodgkin's lymphoma.

Mark R. Goldstein, M.D.

Fountain Medical Court  
Bonita Springs, FL 34135  
markrgoldstein@comcast.net

Luca Mascitelli, M.D.

Comando Brigata Alpina "Julia"  
33100 Udine, Italy

Francesca Pezzetta, M.D.

Ospedale di Tolmezzo  
33028 Tolmezzo, Italy

1. Cheson BD, Leonard JP. Monoclonal antibody therapy for B-cell non-Hodgkin's lymphoma. *N Engl J Med* 2008;359:613-26.

2. Winiarska M, Bil J, Wilczek E, et al. Statins impair antitumor effects of rituximab by inducing conformational changes of CD20. *PLoS Med* 2008;5(3):e64.

**TO THE EDITOR:** We are concerned about a safety issue in the use of rituximab-based immunochemotherapy in patients with B-cell non-Hodgkin's lymphoma and infection with either chronic hepatitis B virus (HBV) or chronic hepatitis C virus (HCV) (or serologic signs of previous contact with HBV virus). These infections are reportedly more prevalent in this group of patients than in the general population.<sup>1,2</sup> Both severe HBV flares and progression to hepatic failure have been reported after the use of rituximab-based immunochemotherapy in patients with B-cell non-Hodgkin's lymphomas<sup>3</sup> and HBV infection. Hepatitis flares have also been reported in patients with HCV infection and non-Hodgkin's lymphoma.<sup>4</sup>

Preemptive treatment of carriers of active or inactive HBV with nucleotide-nucleoside analogues (e.g., lamivudine, adefovir) reduces the incidence of hepatitis flares after treatment with rituximab.<sup>3,5</sup> Such treatment should be strongly considered for patients who test positive for hepatitis B core antibody, negative for hepatitis B surface antibody, or positive for anti-hepatitis B surface antibody. There are no indications that