between 3 and 5 administrative requirements. The most common administrative requirement was to use a specific health department form (17 of 36 bills), followed by the requirement for the parent or guardian to receive education about vaccine risks and benefits (14 bills).

Of 20 states with a current PBE, 5 (25%) saw a bill introduced to restrict exemptions and 1 (5%) saw a bill introduced to expand exemptions. Among the 30 states without a PBE, none saw a bill introduced to restrict exemptions and 13 (43%) saw a bill introduced to expand exemptions. Of the 36 bills introduced, 5 (14%) were categorized as restricting exemptions and 31 (86%) as expanding exemptions. Thirty of the 31 bills to expand exemptions proposed introducing a PBE and 1 proposed removing the requirement for notarization from an existing PBE. None of the bills categorized as expanding exemptions were passed. Three of the 5 bills categorized as restricting exemptions were passed (Washington, California, and Vermont).

Discussion | Exemptions to school immunization requirements continue to be an issue for discussion and debate in many state legislatures. Even though the majority of bills introduced would have expanded exemptions, 14% were designed to strengthen an existing nonmedical exemption. All of the legislative efforts to expand exemptions failed; however, the majority of bills to restrict exemptions passed.

This study has limitations. Although it is based on a comprehensive and multisource database, we may have missed a few of the bills proposed in various state legislatures. However, it is unlikely that this limitation favors 1 type of proposed legislation (ie, restricting vs expanding exemptions) over another.

Saad B. Omer, PhD
Diane Peterson, BS
Eileen A. Curran, MPH
Alan Hinman, MD
Walter A. Orenstein, MD

Author Affiliations: Rollins School of Public Health, Emory University, Atlanta, Georgia (Omer, Curran); Immunization Action Coalition, St Paul, Minnesota (Peterson); Task Force for Global Health, Decatur, Georgia (Hinman); School of Medicine, Emory University, Atlanta, Georgia (Orenstein).

Corresponding Author: Saad B. Omer, MBBS, MPH, PhD, Emory University, 1518 Clifton Rd NE, Room 7017 (CNR Building), Atlanta, GA 30322 (osomer@emory.edu).

Author Contributions: Dr Omer and Ms Curran had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Omer, Hinman, Orenstein.

Acquisition of data: Omer, Peterson.

Analysis and interpretation of data: Omer, Curran, Hinman, Orenstein.

Drafting of the manuscript: Omer, Curran.

Critical revision of the manuscript for important intellectual content: Omer, Peterson, Curran, Hinman, Orenstein.

Statistical analysis: Curran.

Administrative, technical, and material support: Omer, Orenstein.

Study supervision: Omer.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Hinman reported receiving institutional grant funding from the US Centers for Disease Control and Prevention, the Bill & Melinda Gates Foundation, Novartis Vaccines, and the Merck Company Foundation. No other disclosures were reported.

Additional Contributions: We thank Christine Finley, MPH (Vermont Department of Public Health), Catherine Martin, BS (California Immunization Coalition), and Daniel A. Salmon, PhD (Johns Hopkins University Bloomberg School of Public Health), for their input. None received compensation for their contribution.


COMMENT & RESPONSE

Acute Muscle Wasting Among Critically Ill Patients

To the Editor The prospective study by Dr Puthucheary and colleagues1 characterized acute muscle wasting in patients with critical illness. We take exception to the clinical inference that protein delivery was associated with increased muscle wasting. These findings conflict with existing data that higher protein delivery is associated with improved survival, reduced infection, and improved health-related quality of life.2,3

The patients in this study had variable durations of stay in the intensive care unit (ICU) as well as variable and inconsistent delivery of artificial nutrition. The longer a patient is in an ICU, the more likely he or she is to experience adverse outcomes, including loss of muscle mass. Because artificial nutrition is started after the first few days of ICU admission and advanced slowly, patients with longer stays will receive more protein. It would be erroneous to conclude that protein administration causes accelerated loss of muscle mass from such observations. Furthermore, reporting the amount of protein as an area under the curve for 10 days will amplify this result.

Analyses of the association between nutritional intake and subsequent outcomes need to adjust for duration of exposure to artificial nutrition.4 Also, oral nutrition should not be included because the calculation of intake via the oral route is notoriously inaccurate and patients who tolerate oral nutrition are clinically different than those who require artificial nutrition.4 Could the authors reanalyze their data adjusting for duration of exposure to artificial nutrition and excluding oral nutrition?

Furthermore, it would be helpful if the authors described the actual amount of protein and calories received (per kilogram of actual body weight) so readers can judge whether loss of muscle mass occurred in the context of adequate nutrition or underfeeding.

In addition, how did the authors adjust for changes in fluid status among their patients for the measurement of muscle mass? Could the changes in cross-sectional area of the rectus femoris be related to changes in edema?

Daren Heyland, MD
Carrie Earthen, PhD, RD
Charlene Compher, PhD, RD
Letters

Author Affiliations: Clinical Evaluation Research Unit, Kingston, Ontario, Canada (Heyland); Department of Food Science and Nutrition, University of Minnesota, Minneapolis (Earthman); University of Pennsylvania School of Nursing, Philadelphia (Compher).

Corresponding Author: Daren Heyland, MD, Clinical Evaluation Research Unit, 76 Stuart St, Angara 4, Kingston, ON K7L 2V7, Canada (dtkh2@queensu.ca).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Heyland reported receiving grants and personal fees from Fresenius Kabi, Nestle, Baxter, and GlaxoSmithKline; and receiving personal fees from Abbott Nutrition. Dr Earthman reported receiving personal fees for serving on the scientific advisory board on protein for Baxter Healthcare. No other disclosures were reported.


To the Editor Muscle wasting in critically ill patients is both pervasive and detrimental. Dr Puthucheary and colleagues1 attempted to characterize the muscle wasting process and its sequence in critically ill patients from both a clinical and molecular perspective. Unfortunately their report contained several statistical inconsistencies.

Some 95% confidence intervals presented in the body of the article were inconsistent with Figure 2; and some confidence intervals contained zero and were thus inconsistent with statistically significant change despite P values of less than .05. In addition, Figures 2, 3, and 5 appear to be reporting means rather than medians.

Given the large number of candidate predictors (n = 46) and the small sample size (n = 63), the classic approach of bivariable screening followed by stepwise regression may produce too many type I and type II errors to provide reliable inferences.2,3 It is problematic that the regression models used the area under the curve over the first 10 days of organ failure with C-reactive protein, insulin, protein, and calories as independent variables to predict muscle loss by day 10.

Even though all patients in this study were in the ICU for at least 7 days, the area under the curve will increase considerably between day 7 and day 10 while there is significant muscle wasting. Thus, any associations between these predictors and muscle wasting may be spurious due to confounding with ICU length of stay.

Andrew G. Day, MSc

Author Affiliation: Clinical Research Centre, Kingston General Hospital, Kingston, Ontario, Canada.

Corresponding Author: Andrew G. Day, MSc, Clinical Research Centre, 76 Stuart St, Kingston, ON K7L 2V7, Canada (daya@kgh.kari.net).

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.


In Reply The inverse relationship found in our study between protein delivery and muscle wasting was hypothesis generating. Both Dr Heyland and colleagues and Mr Day were concerned that ICU length of stay may have been a confounding variable.

We prespecified an ICU length of stay of greater than 7 days as one of the inclusion criteria, with the primary end point (muscle loss) measured at day 10. Only 7 patients had an ICU length of stay between 7 and 10 days. The areas under the curve for cumulative organ failures over 7 days and 10 days were highly correlated (Figure). Therefore, we were justified in our use of area under the curve over this time frame.

Heyland and colleagues requested further information on nutritional delivery; this is provided in the Table and was similar to the full feeding group in the EDEN trial1 (1900 kcal/d vs 1160 kcal/d in our study), the enteral feeding group in the Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients study,2 and standard clinical practice.3

Regression analysis was not performed on the subgroup of 4 patients that received only parenteral nutrition, which would be inappropriate with such small numbers.

Clinical instability prevented weight measurement on admission; therefore, compartmental water distribution could not be adjusted for or reliably quantified. We agree that muscle edema likely affects ultrasound echogenicity as well as cross-sectional area,4,5 and our data confirmed this with rectus femoris cross-sectional area underestimated the loss in muscle fiber cross-sectional area and ratio of muscle protein to DNA.

Figure. Correlation Between Area Under the Curve (AUC) of Organ Failures Over 7 Days and 10 Days (n=63)

The linear regression of AUC of cumulative organs failed over 10 days (y axis) vs AUC for cumulative organs failed over 7 days (x axis); AUC for 10 days of 1.3859 (95% CI, 1.299-1.473) × AUC for 7 days of 1.446.
Day 7 correctly identified some errors of transcription that affect neither the results nor the discussion. These have been corrected online, and we apologize to the readers. However, certain confidence intervals crossed zero appropriately (eg, those for muscle wasting in patients with single organ failure, who do not show significant muscle loss). The confidence interval for change in muscle atrophy factor crossed zero but was statistically significant because these data were non-normally distributed using the 2-tailed Wilcoxon signed rank test.

Predicting muscle loss was not our study’s primary aim. Because it was unique in design, no expert body of evidence could guide variable selection for multivariable analysis. We thus sought a parsimonious model (with the attendant concern noted by Day) for hypothesis generation for future studies with larger numbers.

Nevertheless, a model controlling for age, sex, organ failure, Acute Physiology and Chronic Health Evaluation II score, insulin received, protein received, total calories received, serum C-reactive protein, calcium, bicarbonate, and ratio of PaO2 to fraction of inspired oxygen (FiO2) confirms the importance of variables found by stepwise regression (odds ratios [ORs] are per unit variable change for 10% loss in rectus femoris cross-sectional area by day 10). There was an OR of 0.904 (95% CI, 0.818-1.000; \( P = .03 \)) for ratio of PaO2 to FiO2, an OR of 1.001 (95% CI, 0.999-1.003; \( P = .10 \)) for C-reactive protein, and an OR of 0.666 (95% CI, 0.453-0.978; \( P = .03 \)) for bicarbonate; c statistic, 0.949 (95% CI, 0.861-0.989); Hosmer-Lemeshow goodness-of-fit test, \( P = .61 \).

Zudin A. Puthucheary, MRCP
Mark J. W. McPhail, MRCP, PhD
Nicholas Hart, BSc, MRCP, PhD, FFICM

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.


**Fetal Outcomes Associated With Metoclopramide Use in Pregnancy**

*To the Editor*—In the study on the use of metoclopramide during pregnancy and the risk of congenital malformations and fetal death,1 explicit details as to the dosage of metoclopramide were not reported. The only stratification made was women receiving 1 prescription vs 2 or more.

Specifically, information was lacking on the dose and the total amount of metoclopramide to which the fetuses were exposed, along with the duration of exposure and the form of administration. Because these factors can affect the molar concentration and the bioavailability of the drug,2 provision of this information is important to evaluate the actual exposure of the fetuses.

The teratogenic effect of many drugs used during pregnancy has been reported as being dependent on dose.3 The analysis of metoclopramide exposure should consider a dose-dependent risk for congenital malformations.

Nikolaos Vrachnis, MD
Dimitrios Zygiouris, MD
Zoe Iliodromiti, MD

**Author Affiliations:** Second Department of Obstetrics and Gynecology, University of Athens Medical School, Athens, Greece (Vrachnis, Iliodromiti); Third Department of Obstetrics and Gynecology, University of Athens Medical School, Athens, Greece (Zygiouris).

---

**Table. Patient Nutritional Delivery Over 10 Days**

<table>
<thead>
<tr>
<th>Type of Nutrition Received</th>
<th>Total (n = 63)</th>
<th>Parenteral Only (n = 4)</th>
<th>Enteral and Parenteral (n = 5)</th>
<th>Enteral Only (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein, g/kg of IBW</td>
<td>6.7 (5.3-8.2)</td>
<td>2.3 (0.72-3.8)</td>
<td>4.2 (2.2-6.3)</td>
<td>7.3 (5.7-8.9)</td>
</tr>
<tr>
<td>Calories, kcal/kg of IBW</td>
<td>158.4 (143.9-172.9)</td>
<td>194.3 (45.7-342.9)</td>
<td>142.6 (92.6-192.5)</td>
<td>157.2 (141.9-172.6)</td>
</tr>
<tr>
<td>Median (range), d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiation of feeding</td>
<td>1 (1-4)</td>
<td>1 (1-2)</td>
<td>2 (1-4)</td>
<td>1 (1-4)</td>
</tr>
<tr>
<td>Full feeding regime</td>
<td>2 (1-10)</td>
<td>2 (1-9)</td>
<td>5 (2-8)</td>
<td>2 (1-10)</td>
</tr>
<tr>
<td>No nutrition delivered</td>
<td>1 (0-6)</td>
<td>1 (0-5)</td>
<td>1 (0-6)</td>
<td>1 (0-6)</td>
</tr>
</tbody>
</table>

Abbreviation: IBW, ideal body weight.