Title: Glucose control: How low should you go with the critically ill? *J Fam Pract*. 2009;58:424-426.
Potential PURL Review Form: Randomized controlled trial

SECTION 1: IDENTIFYING INFORMATION FOR NOMINATED POTENTIAL PURL

1. Citation	NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-1297.
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/entrez/utils/fref.fcgi?PrId=3051&itool=AbstractPlus-def&uid=19318384&db=pubmed&url=http://content.nejm.org/cgi/pmidlookup?view=short&pmid=19318384&promo=ONFLNS19
3. First date published study available to readers	March 24, 2009
4. PubMed ID	19318384
5. Nominated By	Sarah-Anne Schumann
6. Institutional Affiliation of Nominator	University of Chicago
7. Date Nominated	March 24, 2009
8. Identified Through	*New England Journal of Medicine*
9. PURLS Editor Reviewing Nominated Potential PURL	Bernard Ewigman
10. Nomination Decision Date	March 24, 2009
11. Potential PURL Review Form (PPRF) Type	RCT
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Lisa Vargish
14. Reviewer	University of Chicago

Affiliation

15. Date Review Due: April 9, 2009

16. Abstract

BACKGROUND: The optimal target range for blood glucose in critically ill patients remains unclear.

METHODS: Within 24 hours after admission to an intensive care unit (ICU), adults who were expected to require treatment in the ICU for 3 or more consecutive days were randomly assigned to undergo either intensive glucose control with a target blood glucose range of 81 to 108 mg/dL (4.5-6.0 mmol/L) or conventional glucose control, with a target ≤180 mg/dL (≤10.0 mmo/L). The primary end point was death from any cause within 90 days after randomization.

RESULTS: Of the 6104 patients who underwent randomization, 3054 were assigned to undergo intensive control and 3050 to undergo conventional control; data with regard to the primary outcome at day 90 were available for 3010 and 3012 patients, respectively. The 2 groups had similar characteristics at baseline. A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died (odds ratio [OR] for intensive control, 1.14; 95% confidence interval [CI] 1.02-1.28; *P*=0.02). The treatment effect did not differ significantly between operative (surgical) patients and nonoperative (medical) patients (OR for death in the intensive control group, 1.31 and 1.07, respectively; *P*=0.10). Severe hypoglycemia (blood glucose level, ≤40 mg/dL (2.2 mmol/L) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014 (0.5%) in the conventional-control group (*P*<0.001). There was no significant difference between the 2 treatment groups in the median number of days in the ICU (*P*=0.84) or hospital (*P*=0.86) or the median number of days of mechanical ventilation (*P*=0.56) or renal replacement therapy (*P*=0.39).

CONCLUSIONS: In this large, international, randomized controlled trial, intensive glucose control increased mortality among adults in the ICU: a blood glucose target ≤180 mg/dL resulted in lower mortality than a target of 81 to 108 mg/dL. (ClinicalTrials.gov number, NCT00220987) 2009 Massachusetts Medical Society

SECTION 2: CRITICAL APPRAISAL OF VALIDITY

1. Number of patients starting each arm of the study?

3054 intense blood glucose, 3050 in conventional group

2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?

Inclusion: In ICU for 3 days at a time, in 42 hospitals: 38 academic and 4 community, in Australia, New Zealand, and Canada. Patient has an arterial line in situ or placement of an arterial line is imminent as part of routine ICU management.

Exclusion: 1. Age <18 years.
2. Imminent death (cardiac standstill or brain death anticipated in <24 hours) and the treating clinicians are not committed to full supportive care. This is confirmed by a documented treatment-limitation order that exceeds a “not-for-resuscitation” order.
3. Patients admitted to the ICU for treatment of diabetic ketoacidosis or hyperosmolar state.
4. Patients expected to be eating before the end of the day following the day of admission to the ICU.
5. Patients who have previously suffered hypoglycemia without documented

	full neurological recovery. 6. Patients thought to be at abnormally high risk of hypoglycemia (eg, known insulin-secreting tumor or history of unexplained or recurrent hypoglycemia or fulminant hepatic failure). 7. Patient has previously been enrolled in the study. 8. Patient cannot provide prior informed consent and there is documented evidence that the patient has no legal surrogate decision maker and it appears unlikely that the patient will regain consciousness or sufficient ability to provide delayed informed consent. 9. Patient has been in the study ICU or another ICU for 24 hours or more for this admission.
3. Intervention(s) being investigated?	Intense glucose control (between 81 and 108 mg/dL) vs less intense control (≤180 mg/dL).
4. Comparison treatment(s), placebo, or nothing?	Aggressiveness of sugar control.
5. Length of follow-up? Note specified end points, eg, death, cure, etc.	90 days after randomization.
6. What outcome measures are used? List all that assess effectiveness.	Death from any cause within 90 days of randomization or secondary measures: survival time during first 90 days, cause-specific death, duration of mechanical ventilation, renal replacement therapy, and stays in ICU, and hospital tertiary outcomes: death within 28 days, place of death, organ failure, positive blood culture, receipt of red cell transfusion. Primary outcomes looked at in subgroups: operative vs nonoperative, with and without diabetes, with and without severe sepsis, treated with and without steroids, APACHE score less than or more than 25.
7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.	Absolute risk of death was increased by 2.6 with intense sugar treatment; number needed to harm was 38.
8. Study addresses an appropriate and clearly focused question - ***select one***	☒ **Well covered** ☐ Adequately addressed ☐ Poorly addressed ☐ Not applicable
9. Random allocation to comparison groups	Well covered
10. Concealed allocation to comparison groups	Well covered
11. Subjects and investigators kept “blind” to comparison group allocation	Well covered

12. Comparison groups are similar at the start of the trial	Well covered
13. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.	Well covered
14. Were all relevant outcomes measured in a standardized, valid, and reliable way?	Well covered
15. Are patient-oriented outcomes included? If yes, what are they?	Yes: Mortality, length of hospital and ICU stay.
16. What percent dropped out, and were lost to follow up? Could this bias the results? How?	A total of 82 of 6104 patients dropped out: 44 of 3054 (1.4%) from the intense group and 38 of 3050 (1.2%) in the conventional control group. These dropout rates could not bias the results because the numbers were low and similar.
17. Was there an intention-to-treat analysis? If not, could this bias the results? How?	Yes
18. If a multi-site study, are results comparable for all sites?	Yes
19. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?	No
20. To which patients might the findings apply? Include patients in the study and other patients to whom the findings	Any patient with diabetes in ICU setting or any critically ill patient needing sugar control.

may be generalized.

21. In what care settings might the findings apply, or not apply?	ICU
22. To which clinicians or policy makers might the findings be relevant?	Hospitalists.

SECTION 3: REVIEW OF SECONDARY LITERATURE

1. DynaMed excerpts	This article is front and center.
2. DynaMed citation/access date	In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated April 2, 2009. Accessed April 7, 2009.
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)	Basically same as this article.
4. UpToDate excerpts	
5. UpToDate citation/access date	Stapleton RD, Heyland DK. Glycemic control and intensive insulin therapy in critical illness. In: Basow DS, ed. *UpToDate* [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. Last updated January 2009. Accessed April 7, 2009.
6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)	Evidence is mixed; RCTs not done well—meta-analysis shows little difference—right now recommend glucose < 180 mg/dL, although between 80 and 110 mg/dL seems reasonable.
7. PEPID PCP excerpts	None about aggressive glucose control in critically ill patients.
8. PEPID citation/access data	
9. PEPID content updating	1. Do you recommend that PEPID get updated on this topic? No, this topic is current, accurate, and up to date.

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon () that should be updated on the basis of the review?

No, this topic is current, accurate and up to date.

SECTION 4: CONCLUSIONS

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)	1
2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?	
3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by “full scope” family physicians? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)	1
4. If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.	
5. Practice-changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice? Give one number on a scale of 1 to 7 (1=definitely a change from	2

current practice; 4=uncertain; 7=definitely not a change from current practice)	
6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.	Patients' blood sugar in the ICU should not be as aggressively controlled as we once thought. Goal should be more liberal, ≤180 mg/dL.
7. Applicability to a Family Medical Care Setting: Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention? Give one number on a scale of 1 to 7 (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)	7
8. If you coded 4.7 as a 4, 5, 6, or 7, please explain.	Not relevant to primary care.
9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the	2

service, device, drug or other essentials available on the market? Give one number on a scale of 1 to 7 (1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)	
10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.	
11. Clinical meaningful outcomes or patient-oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented? Give one number on a scale of 1 to 7 (1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)	1
12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.	
13. In your opinion, is this a Pending PURL? Give one number on a scale of 1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)	4

Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation

that is applicable to what family physicians do in medical care settings and seems different than current practice. • Applicability in medical setting: • Immediacy of implementation	
14. Comments on your response in 4.13	Not really a PURL for primary care. Could be for ICU, but then I am not sure which range of glucose control that I would recommend for goal.

SECTION 5: EDITORIAL DECISIONS

1. FPIN PURLs editorial decision	Pending PURL—Forward to JFP Editor
2. Follow-up issues for Pending PURL Reviewer	
3. FPIN PURLS Editor making decision	Bernard Ewigman
4. Date of decision	April 8, 2009
5. Brief summary of decision	The standard of care for ICU patients is tight glucose control. This definitive RCT shows that tight control (81-108 mg/dL) actually increases mortality.