



Delfini & Juneja Qualitative Systematic Review Protocol & Process Documentation in Brief

Intensive Insulin Therapy (IIT) for The Treatment of Hyperglycemia in Critically Ill Adults: A Qualitative Systematic Review and Critical Appraisal of the Evidence

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Outcomes

Category	Qualitative Systematic Review
Corresponding Author	Rattan Juneja, MBBS, MD, MRCP Associate Professor of Clinical Medicine Indiana University School of Medicine 541 Clinical Drive CL 365 Indianapolis, IN 46202 USA Email: rajuneja@iupui.edu Tel: +317-2747725 Fax : + 317-2744311
Authors and Contributions	Rattan Juneja MBBS, MD, MRCP: conception, review design, references, data interpretation, writing, final responsibility for submission Michael E. Stuart MD: conception, review design, literature search, quality assessment of individual trials, references, data interpretation, writing, final responsibility for submission Sheri A. Strite: review design, quality assessment of individual trials, references, writing, final responsibility for submission
Funding	Grant from Clarion Health, Indianapolis, Indiana Funder's role is only as employer of Dr. Juneja and grantor to Dr. Stuart and Ms. Strite

Study Aim	To determine the effect of intensive insulin treatment compared to less intensive insulin treatment on mortality and hypoglycemia in adult intensive care unit (ICU) patients and to determine if guideline recommendations for glycemic targets are supported by valid evidence.
Methodology	<ol style="list-style-type: none"> 1. Delfini Group, LLC, methods and judgments for the conduct of this review are similar to those applied for any Delfini purpose or for any Delfini client regardless of funding or of a current or potential future business relationship. 2. Delfini methods for this review are described at length in the body of this document and our based on the Delfini Qualitative Systematic Review Tool.

Key Questions for the IIT Review

The following key questions will be investigated for a population of adult, hospitalized ICU patients:

1. Is there evidence of sufficient robustness in any critically ill populations to justify a specific glycemic control range that is likely to reduce mortality?
2. Is the evidence sufficient to conclude that significant hypoglycemia occurring with tight glycemic control results in clinically meaningful hypoglycemia in any critically ill population?

Literature Search for the IIT Review

Sources

- MEDLINE
- Cochrane Central Register of Controlled Trials, and the
- Cochrane Database of Systematic Reviews

Basis for the Review

In keeping with acceptable evidence-based medicine practice, scientific information from valid and clinically useful clinical practice guidelines or other secondary sources or secondary studies are utilized, where possible, as a basis for each review and updated with new valid and clinically useful primary sources published after the date of the search used for creating the secondary source. (A primary source is the report of an original research study. A secondary source is any source that utilizes primary research information.)

Outcome: Foundation for the review as search and exclusions were deemed appropriate —

Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ*. 2009 Apr 14;180(8):821–7. Epub 2009 Mar 24. Review.

Search Methods

▪ **Outcome: Based on foundation chosen for review plus Delfini’s chosen search sources —**

We searched MEDLINE (March 1, 2008-September 17, 2009, updating our search on December 30, 2009), the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews (March 2008 – December 2009), updating the extensive search conducted for the Griesdale 09 systematic review in which the investigators systematically searched MEDLINE (1966–March 2008), EMBASE (1977–March 2008) and the Cochrane Central Register of Controlled Trials (CENTRAL) (1948–March 2008) for randomized trials examining the effect of intensive insulin therapy on mortality among critically ill patients.¹⁴ In addition, those authors performed a manual search of abstracts from selected conferences held from 2000 to 2008, including conferences of the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, the American Thoracic Society, and the College of Chest Physicians, as well as performing hand-searches of the bibliographies of all relevant trials. We used the PubMed methodological filters, “randomized controlled trials” and “systematic reviews.” No language restrictions were applied. In order to evaluate the trials published in Chinese, we translated the manuscripts into English. In addition, we searched for letters and editorials that were relevant to trials we selected for more detailed review. Our updated search combined the following MeSH terms and text words using the Boolean operator OR: “critical care OR intensive care OR intensive care units OR cardiac care facilities OR critical illness OR postoperative care with text words intensive care OR ICU OR critical care OR CCU OR coronary care OR recovery room OR post anesthetic recovery OR critical illness OR burn unit OR critically ill OR cardiac care) AND (insulin OR blood glucose OR hypoglycemic agents with text words intensive insulin OR glycemic control OR blood glucose OR insulin.”

Outcome: Searches performed on September 17, 2009; updated on December 30, 2009. Searches are documented in search tables for each date and major study type.

Searching and Filtering (Process Used for IIT Systematic Review Modified from these Processes)

Several searches are usually performed applying variations to maximize potentially relevant studies.

Details of the search include search date, search terms, limits (e.g., randomized controlled trial (RCT) or systematic review (SR)) and are documented, as are the number of hits and whether or not each reference is relevant.

Titles and abstracts are evaluated to determine relevancy. Studies found to have fatal flaws identifiable within the title or abstract are excluded at this stage and the reason for exclusion is documented.

Specific exclusion criteria are found in individual search tables included in review documentation. Generally exclusion criteria at a minimum: studies not published in the English language, studies not relevant to the question, animal studies, editorials, opinion pieces, abstracts without full documentation of research, narrative reviews, observational studies for determining efficacy of interventions, studies deemed not useful for clinical questions (see below for description):

- Clinically useful studies are defined as those with clinically meaningful size of benefits in prespecified outcomes of importance to patients (defined as “mortality, morbidity, symptom relief, emotional and physical functioning and health-related quality-of-life”).
- Studies reporting pre-specified intermediate outcomes are excluded unless a strong valid and useful chain-of-evidence has been established between intermediate markers and resulting clinically significant outcomes, as defined above, with clinically meaningful size of benefits

Exceptions may be made as deemed necessary to support good EBM practice such as papers dealing with reports of harms, observations with all-or-none-results and certain public health interventions which may be deemed as having experimental characteristics or for which prognostic factors are so broad as to render confounding unlikely.

- Example: Observational data may be convincing for emergency surgery for ruptured aortic aneurysms, the use of antibiotics in acute meningitis or results of public health water purification efforts. In these instances, many or all affected individuals were affected or died and, after the intervention, many or most were prevented from being affected or survived.

Study Selection for the IIT Review

Inclusion criteria for our assessment of the effect of IIT compared to less intensive insulin treatment on mortality and hypoglycemia will be randomized controlled trials of hyperglycemic hospitalized adults receiving IIT in ICU settings. We will assess the methodological quality for risk of bias in studies chosen for review. One reviewer will screen titles and abstracts and, in some cases, full text for exclusions.

We will exclude trials available in abstract only, are unpublished (e.g., presented at meetings), focus on comparisons of intra-operative insulin treatments rather than intensive insulin treatment in the ICU, contain fewer than 25 subjects in any of the study arms, exclude 20% or more of randomized patients from the analysis,^[1] or do not report mortality.

Outcome: Included and excluded studies are documented in tables.

Quality Assessment and Rating of the Body of Evidence for the IIT Review

Two reviewers will assess the methodological quality of included studies by evaluating selection, performance, attrition and assessment bias along with other threats to validity using a comprehensive checklist, details of which have been previously published.^[2] The checklist contains all the elements that can be found in the Cochrane Collaboration tool for assessing risk of bias, but extends the Cochrane tool to assess additional biases.^[3] Reasons for exclusion of studies initially selected as potentially relevant will be reviewed by all three reviewers. Each study will be graded using the following system: grade A = valid and useful for informing decisions; grade B = possibly valid and useful; grade B-U = possible to uncertain validity and usefulness; grade U = uncertain validity and/or usefulness.) Any disagreements in assigned study grades will be resolved by re-review and discussion until unanimity is reached. If unanimity cannot be reached, we will default to the lowest evidence grade. Relevant information from each full text article will be extracted by one or two reviewers. Extracted data will include study aim, setting, size, outcome measures, participant characteristics, details of generation of the randomization sequence and concealment of allocation of subjects to their groups, interventions, blinding, loss of data and other threats to validity. Our review will focus on mortality and

hypoglycemia outcomes reported in the trials with evidence grades of B-U or higher which correspond to medium or low risk of bias in the AHRQ EHCP approach. We will exclude studies graded U because of the high risk of bias.

We will document the overall quality of the evidence by applying the domains recently selected by the Agency for Healthcare Research and Quality (AHRQ) and the Effective Health Care Program (EHCP) group.^[4] These domains were selected by AHRQ EHCP after reviewing choices made by the U.S. Preventive Services Task Force (USPSF)^[5], the GRADE working group^[6] and other evidence-based practice centers.^[7, 8] Briefly, The AHRQ EHCP approach assesses the risk of bias, consistency, directness and precision for each outcome or comparison of interest (in some instances, paraphrased below):

- Bias is scored as low, medium, or high risk of bias. Each study is scored based on study design and conduct, and the aggregate of studies is scored for an overall “risk of bias” score.
- Consistency (the degree of similarity of effect sizes of included studies) is scored as consistent, inconsistent, or unknown/not applicable.
- Directness is the linkage between the intervention and health outcomes scored as direct or indirect (meaning intermediate or surrogate outcome measures).
- Precision concerns the ability to draw a clinically useful conclusion from the confidence intervals. An imprecise estimate, for example, is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g., favoring both the interventions being compared).

The overall level of evidence (LOE) for each outcome of interest utilized by the AHRQ and EHCP group includes three grades—high, moderate and inconclusive. For example, if the LOE is high, further research is unlikely to change confidence in the estimate of effect. If evidence is unavailable or does not permit a conclusion, the outcome in the AHRQ EHCP system is graded as inconclusive. For this review, we modified this grading system for overall LOE by adding a fourth category —“borderline” to increase clarity as we believe “moderate” is not precise enough to address evidence of borderline usefulness. We will grade the overall LOE for mortality and hypoglycemia as “high” if we find more than one grade B (valid and possibly useful) study reporting consistent results, “moderate” if we find at least one grade B study, “borderline” if we find at least two grade B-U (possible to uncertain validity and usefulness) studies with consistent findings and “inconclusive” if we find single grade B-U studies or studies with conflicting results or only grade U studies (uncertain usefulness or validity).

Outcome: Tables were created for critical appraisals, table of included studies and results.

Delfini Evidence Grading Scale

Grade of Usability	Strength of Evidence Advice
● Grade A: Useful	<p>Grades can be applied to individual studies, to conclusions within studies, a body of evidence or to secondary sources such as guidelines or clinical recommendations. General advice is provided below.</p> <p>The evidence is strong and appears sufficient to use in making health care decisions – it is both valid and useful (e.g., meets standards for clinical significance, sufficient magnitude of effect size, physician and patient acceptability, etc.)</p> <p>Advice: Studies achieving this grade should be outstanding in design, execution and reporting with useful information to aid clinical decision-making, enabling reasonable certitude in drawing conclusions.</p> <p>For a body of evidence: Several well-designed and conducted studies that consistently show similar results</p> <ul style="list-style-type: none"> For therapy, screening, prevention and diagnostic studies: RCTs. In some cases a single, large well-designed and conducted RCT may be sufficient; however, without confirmation from other studies results could be due to chance, undetected significant biases, fraud, etc. In such instance the study might receive a Grade A, but the Strength of the Evidence should include a cautionary note. For natural history and prognosis: Cohort studies
⊙ Grade B: Possibly Useful	<p>The evidence appears potentially strong and is probably sufficient to use in making health care decisions - some threats to validity were identified</p> <p>Advice: Studies achieving this grade should be of high quality in design, execution and reporting with non-lethal threats to validity and with sufficiently useful information to aid clinical decision-making, enabling reasonable certitude in drawing conclusions.</p> <p>For a body of evidence: The evidence is strong enough to conclude that the results are probably valid and useful (see above); however, study results from multiple studies are inconsistent or the studies may have some (but not lethal) threats to validity.</p> <ul style="list-style-type: none"> For therapy, screening, prevention and diagnostic studies: RCTs. In some cases a single, large well-designed and conducted RCT may be sufficient; however, without confirmation from other studies results could be due to chance, undetected significant biases, fraud, etc. In such instance the study might receive a Grade A, but the Strength of the Evidence should include a cautionary note. Also for diagnosis, valid studies assessing test accuracy for detecting a condition when there is evidence of effectiveness from valid, applicable RCTs. For natural history and prognosis: Cohort studies
● Grade B-U: Possible to uncertain usefulness	<p>The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U.</p> <p>Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.</p>
○ Grade U: Uncertain Validity and/or Usefulness	<p>There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.</p> <ul style="list-style-type: none"> Uncertain Validity: This may be due to uncertain validity due to methodology (enough threats to validity to raise concern – our suggestion would be to not use such a study in most circumstances) or may be due to conflicting results. Uncertain Usefulness: Or this may be due to uncertain applicability due to results (good methodology,

	<p>but questions due to effect size, applicability of results when relating to biologic markers, or other issues). These latter studies may be useful and should be viewed in the context of the weight of the evidence.</p> <ul style="list-style-type: none">• Uncertain Validity and Usefulness: This is a combination of the above.• Uncertainty of Author: If the author has reached a conclusion that the findings are uncertain, doing a critical appraisal is unlikely to result in a different conclusion. The evidence leaves us uncertain regardless of whether the study is valid or not. Critical appraisal is at the discretion of the reviewer.
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Data Analysis for the IIT Review

Results will be reported as a range of effect sizes for mortality and hypoglycemia as reported in the original trials along with reported P values and/or 95% confidence intervals (CIs).

CHECKLIST FOR EVIDENCE TABLES FOR INCLUDED TRIALS: CRITICAL APPRAISALS AND RATINGS OF PRIMARY STUDIES INCLUDED IN REVIEW—TO INCLUDE THE FOLLOWING

Author Yr PMID
Evidence Grade
Aim
Setting
Intervention
Details of insulin administration, blood sugar monitoring
Duration
Outcome measures
Study size and loss/withdrawal of subjects
Comparator
Randomization
Concealed allocation
Blinding including assessors
Sameness of groups
Population at baseline
Disease spectrum, APACHE II Score, % Diabetics
Co-interventions
Type of Analysis
Other validity issues
Mortality Results
Hypoglycemia Results
Other notes
Funder/Sponsorship
Evidence Statement based on study
Reviewer Conclusions

Summarizing the Evidence

An evidence summary or synthesis including efficacy and safety based on the reviewed studies is created. Delfini records those outcomes determined, in Delfini’s judgment, to be clinically meaningful.

Efficacy of Treatments

With rare exception, only valid and clinically useful conclusions from randomized controlled trials are used for questions of efficacy of interventions of therapy, screening or prevention (grades A, B and BU). With rare exception, studies or conclusions receiving a Grade U are generally treated by Delfini as hypothesis-generating only and are not graded as of higher quality than judgments of experts. They are not used for drawing cause and effect conclusions, but are regarded as if the studies had never been conducted – meaning that Delfini believes it is completely reasonable to rely on clinical judgment in the absence of valid and clinically useful evidence from medical literature as the basis for clinical judgments or recommendations. It is, however, important to grade or state the strength of the recommendation with clarity about whether the recommendation is based on valid and clinically useful evidence or expert opinion.

Safety (Process Used for IIT Systematic Review Modified from these Processes)

Delfini performs safety reviews using methods suitable for the work scope of the project.

This review will hypoglycemia only including trials graded B-U formally reporting hypoglycemia outcomes.

References

- ¹ Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence based medicine: how to practice and teach EBM. New York: Churchill Livingstone, 1997.
- ² Strite SA, Stuart ME, Urban S. Process steps and suggestions for creating drug monographs and drug class reviews in an evidence-based formulary system. *Formulary*. April 2008;43:135–145.
- ³ *Cochrane Handbook for Systematic Reviews of Interventions 5.0.1*. Cochrane Collaboration; 2008: chap 8. Available at <http://www.cochrane-handbook.org/>. Accessed 9/11/09.
- ⁴ Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. *J Clin Epidemiol*. 2009 Jul 10.
- ⁵ Sawaya GF, Guirguis-Blake J, LeFevre M, Harris R, Petitti D; U.S. Preventive Services Task Force. Update on the methods of the U.S. Preventive Services Task Force: estimating certainty and magnitude of net benefit. *Ann Intern Med*. 2007 Dec 18;147(12):871-5.
- ⁶ Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924e6.
- ⁷ West S, King V, Carey TS, et al. Systems to Rate the Strength of Scientific Evidence. Evidence Report/ Technology Assessment No. 47 (Prepared by the Research Triangle Institute- University of North Carolina Evidence-based Practice Center under Contract No. 290-97-0011). AHRQ Publication No. 02-E016. Rockville, MD: Agency for Healthcare Research and Quality; 2002.
- ⁸ Treadwell JR, Tregear SJ, Reston JT, Turkelson CM. A system for rating the stability and strength of medical evidence. *BMC Med Res Methodol* 2006;6:52.