Inclusion of studies to be re-assessed by panel members in Summer 2009

10.4 Intensive Insulin Therapy — May 27th 2009

Recommendation:

We recommend that hyperglycemia (blood sugars > 10 mmol/L) be avoided in all critically ill patients. Based on the NICE-SUGAR study and a recent meta-analysis, we recommend a blood glucose target of around 8.0 mmol/L (or 7-9 mmol/L), rather than a more stringent target range (4.4 to 6.1 mmol/L) or a more liberal target range (10 to 11.1 mmol/L).

Discussion:

The committee noted the results of the recently published meta-analysis [1] and the results of the largest multicentre trial, the NICE-SUGAR study [2]. Whilst the meta-analysis noted a possible treatment benefit with tight glycemic control in surgical patients, this was not supported by the subgroup analysis in the NICE-SUGAR study which showed a significant increase in mortality in surgical patients. Furthermore, the NICE-SUGAR trial is more likely to be generalizable to Canada or other settings that use a predominantly enteral-based feeding approach. It was also noted that the positive signal in surgical patients in the CMAJ meta-analysis was primarily driven by two studies, the reproducibility of these results was considered questionable given the nature of the accompanying nutritional strategy used in one study [3] and the single centre nature of the other study [4]. Given this the committee reversed its prior recommendation and agreed that tight glycemic control (4.4 to 6.1 mmol/L) is no longer recommended for surgical patients. Instead the committee recommended that the target range be the resultant blood glucose range in the NICE SUGAR study i.e. 8.0 mmol/L (7.0-9.0 mmol/L). This range avoids hyperglycemia, while minimizing the risk of both iatrogenic hypoglycemia and other harms associated with a lower blood glucose target. The committee noted that insulin protocols (either paper or computerized) were used to achieve glycemic control in the reviewed studies but did not make a recommendation as to how best to achieve good glycemic control.

(1) Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. 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

(2) Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ for the NICE-SUGAR Study Investigators,. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009 Mar 26;360(13):1283-97

(3) Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001 Nov 8;345(19):1359-67

(4) He W, Zhang TY, Zhou H, Li T, Zhao JY, Zhao D, Liu XH, Hou J, Wang C, Xu Y. [Impact of intensive insulin therapy on surgical critically ill patients] [Article in Chinese] Chinese Journal of Surgery [Zhonghua Wai Ke Za Zhi. 2007 Aug 1;45(15):1052-4.

Inclusion of studies to be re-assessed by panel members in Summer 2009

	Definition	Score 0, 1, 2 or 3
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	**0**
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	**1**
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of VAP--a higher score indicates presence of more of these features in the trials appraised	**2 (pending)**
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	**2**
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	**2**
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	**2**
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre =1, moderate likelihood i.e. multicentre with limited patient population or practice setting =2, high likelihood i.e. multicentre, heterogenous patients, diverse practice settings =3.	**3**
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	**3**
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	**2**
Safe	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	**1**

Inclusion of studies to be re-assessed by panel members in Summer 2009

10.4 Intensive Insulin Therapy — May 27th 2009

Question: Does tight blood sugar control result in better outcomes in the critically ill adult patient?

Summary of evidence: There was a recent meta-analysis of 26 randomized controlled trials (Greisdale 2009) that was reviewed. Subsequent to the publication of the meta-analysis, the data from two of the included trials (Bilotta 2007 and 2008) were replaced by the data from a more recent trial (Bilotta 2009). Of the remaining 25 trials, four of these were in surgical patients (Van den Berghe 2001, Grey 2004, He 2007 and Bilotta 2009) 15 were in mixed ICUs and 5 were in medical patients. The target ranges of blood sugars in the intervention group varied from 4.0–6.0 to 4.4-8.3 mmol/L.

Mortality: When the data from all the studies were aggregated, intensive insulin therapy had no effect on mortality (RR 0.93, 95% CI 0.83–1.04), significant heterogeneity was present between studies p = 0.005. Subgroup analyses showed that intensive insulin had no effect on mortality in medical patients RR 1.00 (95% CI 0.78–1.28) or mixed ICU patients RR 0.99 (95% CI 0.86–1.12) but there was a significant reduction in surgical patients RR 0.63 (95% CI 0.44–0.91) (p = 0.02). Refer to Greisdale CMAJ 2009 for meta-analysis figure.

Hypoglycemia: Fourteen trials provided sufficient data on hypoglycemic events and intensive insulin therapy was associated with a significant increase in incidence of hypoglycemia RR was 6.0 (95% CI 4.5–8.0), with some evidence of heterogeneity between studies (*p* = 0.08) (refer to Greisdale CMAJ 2009 for meta-analysis figure).

Infections, Length of Stay, Duration of Ventilation: Pending official data abstraction and finalization from panel members.

Conclusions:

1) Intensive insulin therapy resulting in a target blood sugar range of 4.4 to 6.1 mmol/L has no effect on mortality.
2) Intensive insulin therapy resulting in a target blood sugar range of 4.4 to 6.1 mmol/L is associated with a higher risk of hypoglycaemia.
3) Effect on intensive insulin therapy on infectious complications, length of stay and duration of ventilation: pending.

Inclusion of studies to be re-assessed by panel members in Summer 2009

Table 1. Randomized studies evaluating intensive insulin therapy in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡	
1) Van Den Berghe 2001	ICU ventilated (mainly surgical) N=1548	C.Random: yes ITT: yes Blinding: no (11)	Intensive insulin therapy (bl. glucose range between 4.4 –6.1 mmol/L) vs. Conventional (bl. glucose range between 10-11.1 mmol/L)	**Intensive insulin** **ICU** 35/765 (5) **Hospital** 55/765 (7)	**Conventional** **ICU** 63/783 (8) **Hospital** 85/783 (11)	**Intensive insulin** 32/765 (4)	**Conventional** 61/783 (8)
2) Grey 2004	Surgical ICU needing treatment for hyperglycemia N = 61	C.Random: no ITT: no Blinding: no (4)	Strict insulin therapy (bl. glucose range between 4.4 to 6.6 mmol/L) vs. Conventional (blood sugar range between 10-12 mmol/L) in patients requiring treatment for hyperglycemia (bl. glucose > 7.7 mmol/L).	**Intensive insulin** **Hospital** 4/34 (11)	**Conventional** **Hospital** 6/27 (27)	**Intensive insulin** 21/34 (26)	**Conventional** 20/27 (38)
3) Bland 2005	Medical ICU patients N = 10	C.Random: no ITT: no Blinding: no (5)	Intensive insulin therapy (bl. glucose range between 4.4 to 6.1 mmol/L) vs. Conventional (bl. glucose range between 10-11.1 mmol/L) and insulin given if bs > 11.1 mmol/L	**Intensive insulin** **28 day** 1/5 (20)	**Conventional** **28 day** 2/5 (40)	**Intensive insulin** NR	**Conventional** NR
4) Yu 2005* **	Patients with sepsis/ organ failures N = 55	C.Random: no ITT: yes Blinding: no (6)	Intensive insulin therapy (bl. glucose range between 4.4 to 6.1 mmol/L) vs. Conventional (bl. glucose range between 10-11.1 mmol/L) and insulin given if bs > 11.9 mmol/L	**Intensive insulin** **ICU** 3/28 (11) **Hospital** 4/28 (14)	**Conventional** **ICU** 4/27 (15) **Hospital**4/27 (15)	**Intensive insulin** **Antibiotic days** 10 **pts. with bacteria in blood** 8/28 (29)	**Conventional** **Antibiotic days** 17 **pts. with bacteria in blood** 13/27 (48)
5) Van den Berghe 2006	Medical ICU patients expected to stay in ICU ≥ 3 days N = 1200	C.Random: yes ITT: yes Blinding: no (12)	Intensive insulin therapy (bl. glucose range 4.4-6.1 mmol/L) vs. Conventional (blood sugar range 10-11mmol/L and insulin given if bl. glucose >12 mmol/L)	**Intensive insulin** **ICU** 144/595 (24) **Hospital** 222/595 (37) **28 day** 178/595 (30)	**Conventional** **ICU** 162/605 (27) **Hospital** 242/605 (40) **28 day** 182/605 (30)	**Intensive insulin** NR **No effect on Bacteremia (reduction was 7-8% in intensive insulin group)**	**Conventional** NR
6) Wang 2006* **	Mixed ICU patients N = 116	C.Random: not sure ITT: yes Blinding: no (5)	Intensive insulin therapy (bl. glucose range 4.4-6.1 mmol/L) vs. Conventional (bl. glucose range 10-11.1 mmol/L) and insulin given if bs > 11.9 mmol/L	**Intensive insulin** **Hospital** 7/58 (12.1)	**Conventional** **Hospital** 26/58 (45)	**Intensive insulin** NR	**Conventional** NR

Inclusion of studies to be re-assessed by panel members in Summer 2009

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡	
7) Mitchell 2006	Mixed ICU patients N = 70	C.Random: yes ITT: yes Blinding: no (9)	Intensive insulin therapy (bl. glucose range 4.4-6.1 mmol/L) vs. Conventional (bl. glucose range 10-11.1 mmol/L)	**Intensive insulin** **ICU** 7/35 (20) **Hospital** 9/35 (26)	**Conventional** **ICU** 2/35 (6) **Hospital** 3/35 (9)	**Intensive insulin** NR	**Conventional** NR
8) Farah 2007	Mixed ICU patients N = 89	C.Random: not sure ITT: no Blinding: no (3)	Intensive insulin therapy** (bl. glucose range 6.1-7.8 mmol/L) vs. Conventional (insulin given to keep bl. glucose range 7.8 to 11.1 mmol/L)	**Intensive insulin** **ICU** 16/41 (39) **28 day** 19/41 (46)	**Conventional** **ICU** 16/48 (31) **28 day** 26/48 (54)	**Intensive insulin** **All infections** 30/41 (73) **Pneumonia** 24/41 (59)	**Conventional** **All infections** 38/48 (79) **Pneumonia** 28/48 (58)
9) McMullin 2007	Medical ICU patients N = 20	C.Random: yes ITT: yes Blinding: no (9)	Intensive insulin therapy (bl. glucose range 5-7 mmol/L) vs. Conventional (bl. glucose range 8-10mmol/L)	**Intensive insulin** **ICU** 2/11 (18) **Hospital** 6/11 (55)	**Conventional** **ICU** 4/9 (44) **Hospital** 4/9 (44)	**Intensive insulin** 3/11 (27)	**Conventional** 2/9 (22)
10) Brunkhorst 2008	Septic shock patients from 18 ICUs N = 537	C.Random: not sure ITT: yes Blinding: no (10)	Intensive insulin therapy** (bl. glucose range 4.0-6.1 mmol/L) vs. Conventional (blood sugar range 10-11.1 mmol/L and insulin given if bl. glucose >11.1 mmol/L)	**Intensive insulin** **28 day** 61/247 (25) **90** day 98/247 (38)	**Conventional** **28 day** 75/289 (26) **90 day** 102/288 (35)	**Intensive insulin** NR	**Conventional** NR
11) Arabi, 2008	Mixed ICU patients with blood sugars > 6.1 mmol/L N = 523	C.Random: yes ITT: yes Blinding: no (9)	Intensive insulin therapy (bl. glucose range 4.4-6.1 mmol/L) vs. Conventional (bl. glucose range 10-11.1 mmol/L)	**Intensive insulin** **ICU** 36/266 (13.5) **Hospital** 72/266 (27)	**Conventional** **ICU** 44/257 (17) **Hospital** 83/257 (32)	**Intensive insulin** **% sepsis** 98/266 (37) **New infections per 1000 days** 56	**Conventional** **% sepsis** 105/257 (41) **New infections per 1000 days** 59
12) Devos unpublished*	Patients from 21 mixed ICUs N = 1101	C.Random: yes ITT: yes Blinding: no (9)	Intensive insulin therapy (bl. glucose range 4.4-6.1 mmol/L) vs. Conventional (bl. glucose range 7.8 to 10 mmol/L)	**Intensive insulin** **ICU** 92/550 (16.7) **Hospital** 107/550 (19.5)	**Conventional** **ICU** 84/551 (15.2) **Hospital** 89/551(16.2)	**Intensive insulin** **Days on antibiotics** 3.9 ± 7.0	**Conventional** **Days on antibiotics** 3.7 ± 6.7
13) De La Rosa 2008	Mixed ICU Patients N = 504	C.Random: yes ITT: yes Blinding: no (11)	Intensive insulin therapy (bl glucose range 4.4-6.1 mmol/L) vs. Conventional (bl glucose range 10-11.1 mmol/L)	**Intensive insulin** **ICU** 84/254 (33) **Hospital** 102/254 (40) **28 day** 93/254 (37)	**Conventional** **ICU** 78/250 (31) **Hospital** 96/250 (38) **28 day** 81/250 (38)	**Intensive insulin** **all infections** 33% **Pneumonia** 43/254 (16.9)	**Conventional** **all infections** 27% **Pneumonia** 55/250 (22)

Inclusion of studies to be re-assessed by panel members in Summer 2009

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡	
14) Iapichino 2008	Septic patients from 3 ICUs N = 90	C.Random: no ITT: no Blinding: no (8)	Intensive insulin therapy (bl glucose range 4.4-6.1 mmol/L) vs. Conventional (bl glucose range 10- 12 mmol/L)	**Intensive insulin** **ICU** 8/36 (22) **90 day** 13/36 (36)	**Conventional** **ICU** 6/36 (17) **90 day** 11/36 (31)	**Intensive insulin** NR	**Conventional** NR
15) Henderson, 2005	Mixed ICU patients N=67	Pending	Intensive insulin therapy [bl. glucose range 5-7mmol/L] vs Conventional insulin therapy [bl. glucose range 9-11mmol/L]	**Intensive Insulin** **28 day** 4/32 (13)	**Conventional** **28 day** 5/35 (14)	NR	NR
16) Walters 2006	Acute ischemic stroke patients n=25	Pending	Rigorous glycemic control [bl glucose range 5-8 mmol/L] vs Conventional [IV insulin infusion if bl. glucose > 15mmol/L]	**Intensive Insulin** **ICU** NR **3 week** 1/13 (8)	**Conventional** **ICU** NR **3 week** 0/12 (0)	**Intensive Insulin** NR	**Conventional** NR
17) de Azevedo 2007	Patients with neurological injury N=206	Pending	Intensive insulin therapy [continuous IV to maintain bl. glucose range 80-120 mg/dL vs Conventional [patients received insulin if bl. glucose was higher than 180 mg/dL]	**Intensive Insulin** **ICU** 8/31 (26)	**Conventional** **ICU** 6/17 (35)	**Intensive Insulin** **Pneumonia** 9/31 (30) **UTI** 3/31 (10)	**Conventional** **Pneumonia** 3/17 (18) **UTI** 1/17 (6)
18) He 2007	Surgical ICU N = 188	Pending	Intensive insulin therapy [BG 4.44 – 6.11 mmol/L] vs Medium [BG 6.7 – 8.3 mmol/L] vs High [BG 10.0 – 11.1 mmol/L]	**Intensive Insulin** 7/150 (5)	**Conventional** 6/38 (16)	TBD	TBD
19) Oksanen 2007	Medical ICU N = 90	Pending	Strict glucose control [4-6 mmol/L] vs. Moderate glucose control [6-8 mmol/L]	**Intensive Insulin** **30 day** 12/39 (33)	**Conventional** **30 day** 18/51 (35)	NR	NR
20) Bruno 2008	Patients with cerebral infarction from 5 ICUs N=46	Pending	Aggressive insulin treatment [continuous IV to maintain bl. glucose range 5.0 - 7.2 mmol/L] vs Usual care [subQ insulin administered QID]	**Intensive Insulin** **3 months** 2 (7)	**Conventional** **3 months** 0 (0)	**Intensive Insulin** NR	**Conventional** NR
21) He 2008	Mixed ICU N = 122	Pending	Intensive insulin therapy [BG 4.4 – 6.1 mmol/L] vs High [BG 10.0 – 11.1 mmol/L]	**Intensive Insulin** 16/58 (28)	**Conventional** 29/64 (45)	TBD	TBD
22) Mackenzie 2008	Mixed ICU patients from 2 ICUs N= 240	Pending	Tight bl. glucose range 4-6 mmol/L, threshold > 6 mmol/L] vs Conventional glycaemic control [range 10-11 mmol/L, threshold >11mmol/L]	**Intensive Insulin** **ICU** 23 (19) **Hospital** 39 (32)	**Conventional** **ICU** 27 (23) **Hospital** 47 (40)	**Intensive Insulin** **Days of septic shock** 0 (0,0)	**Conventional** **Days of septic shock** 1 (0, 3)

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Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡	
23) Finfer (NICE SUGAR) 2009	Mixed ICU N = 6022	Pending	Intensive insulin therapy [BG range 4.5-6.0 mmol/L] vs Conventional insulin therapy [BG range < 10 mmol/L]	**Intensive Insulin** **ICU** 546/3010 (18) **Hospital** 220/3010 (7) **28 day** 829/3010 (28) **90 day** 670/3010 (22)	**Conventional** **ICU** 498/73012 (17) **Hospital** 197/3012 (7) **28 day** 751/3012 (25) **90 day** 627/3012 (21)	**Blood culture + for pathogens** 387/3014 (13)	**Blood culture + for pathogens** 372/3011 (15)
24) Bilotta 2009	Neurosurgical ICU undergoing elective or emergency surgery N = 483	Pending	Intensive insulin therapy [BG 4.44 – 6.11 mmol/L] vs Conventional [BG < 11.94] for 14 days or until discharge	**Intensive Insulin** 6 months 63 (26)	**Conventional** 6 months 68 (28)	**Intensive Insulin # patients ≤ 1 infection** 62 (26)	**Conventional # patients ≤ 1 infection** 95 (40)
25) Zhang	Mixed ICU N = 338	Pending	Intensive insulin therapy [BG 4.44 – 6.11 mmol/L] vs Conventional [BG 7.2 – 8.3 mmol/L]	**Intensive Insulin** 4/168 (2)	**Conventional** 6/170 (3)	TBD	TBD

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Study	LOS days		Ventilator days		Other
1) Van Den Berghe 2001	**Intensive insulin** **ICU** 7 ± 11* **Hospital** 23 ± 32 *	**Conventional** **ICU** 9 ± 15* **Hospital** 23 ± 28 *	**Intensive insulin** 5 ± 11*	**Conventional** 7 ± 15*	**Intensive insulin** **Conventional** **Hypoglycemia** 39/765 (5) 6/783 (<1)
2) Grey 2004	**Intensive insulin** **ICU** 33.4 ± 68.3	**Conventional** **ICU** 24.5 ± 19.4	**Intensive insulin** NR	**Conventional** NR	**Intensive insulin** **Conventional** **Hypoglycemia** 32% 74%
3) Bland 2005	**Intensive insulin** NR	**Conventional** NR	**Intensive insulin** NR	**Conventional** NR	**Intensive insulin** **Conventional** **Severe hypoglycemia** 1/5 (20) 1/5 (20) **Moderate hypoglycemia** 4/5 (80) 3/5 (60)
4) Yu 2005* **	**Intensive insulin** NR	**Conventional** NR	**Intensive insulin** **Days of ventilation** 10 (9)	**Conventional** **Days of ventilation** 17 (10)	**Intensive insulin** **Conventional** **Hypoglycemia** 3/28 (11) 0/27
5) Van den Berghe 2006	**Intensive insulin** **ICU** 8 ± 9* **Hospital** 31 ± 42*	**Conventional** **ICU** 10 ± 12* **Hospital** 36 ± 60*	**Intensive insulin** 6 ± 9*	**Conventional** 8 ± 12*	**Intensive insulin** **Conventional** **Hypoglycemia** More often in the intensive group
6) Wang 2006* **	**Intensive insulin** **ICU** 9.14 ± 5.45 (58)	**Conventional** **ICU** 12.88 ± 8.29 (58)	**Intensive insulin** 6.02 ± 5.47 (58)	**Conventional** 9.21 ± 8.56 (58)	**Intensive insulin** **Conventional** **Severe Hypoglycemia** 5/35 (14) 0/35
7) Mitchell 2006	**Intensive insulin** **ICU** 5 (3-8)	**Conventional** **ICU** 4 (3-9)	**Intensive insulin** 15 (7.5-28.5)	**Conventional** 18 (11-31.5)	**Intensive insulin** **Conventional** **Patients with hypoglycemia** 6/58 (10) 2/58 (3)
8) Farah 2007	**Intensive insulin** **ICU** 7 ± 4.9 (41)	**Conventional** **ICU** 8 ± 4.85 (48)	**Intensive insulin** NR	**Conventional** NR	**Intensive insulin** **Conventional** **Hypoglycemic events** 23/41 (56) 23/48 (48)
9) McMullin 2007	**Intensive insulin** **ICU** 15 (6-25) **Hospital** 21 (17-40)	**Conventional** **ICU** 6 (4-20) **Hospital** 16 (10-23)	**Intensive insulin** NR	**Conventional** NR	**Intensive insulin** **Conventional** **Severe Hypoglycemia** 4/11 (36) 1/9 (11)
10) Brunkhorst 2008	**Intensive insulin** **ICU** 16 (8-30)	**Conventional** **ICU** 14 (7-25)	**Intensive insulin** **Vent free days** 3 (1-7)	**Conventional** **Vent free days** 3 (1-6)	**Intensive insulin** **Conventional** **Hypoglycemia** 42/247 (17) 12/280 (4)
11) Arabi, 2008	**Intensive insulin** **ICU** 9.6 ± 8.5 (266) **Hospital** 54.1 ± 84.1(266)	**Conventional** **ICU** 10.8 ± 11.3 (257) **Hospital** 57.5 ± 77.1(257)	**Intensive insulin** 8.3 ± 7.9 (266)	**Conventional** 9.7 ± 11.0 (257)	**Intensive insulin** **Conventional** **Patients with hypoglycemia** 76/266 (29) 8/257 (3)
12) Devos (Preiser) unpublished*	**Intensive insulin** **ICU** 6 (3-13) **Hospital** 16 (11-30)	**Conventional** **ICU** 6 (3-13) **Hospital** 16 (11-29)	**Intensive insulin** **Patient days** 2532	**Conventional** **Patient days** 2572	**Intensive insulin** **Conventional** **Hypoglycemia** 14.5 % 3.9 %

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Study	LOS days		Ventilator days		Other
13) De La Rosa 2008	**Intensive insulin** **ICU** 6 (3-12)	**Conventional** **ICU** 6 (3-11)	**Intensive insulin** 6 (2-10)	**Conventional** **5 (2-9)**	**Intensive insulin** **Conventional** **Hypoglycemia** 8.3% 0.8%
14) Iapichino 2008	**Intensive insulin** **ICU** 16 (8.1-28.5)	**Conventional** **ICU** 13 (6.5-23.5)	**Intensive insulin** NR	**Conventional** NR	**Intensive insulin** **Conventional** **Severe Hypoglycemia** 8/36 (22) 3/36 (8)
15) Henderson, 2005	**Intensive insulin (Median, range)** **ICU** 7.42 (5.12-12.72) **Hospital** 22 (13-40.5)	**Conventional (Median, range)** **ICU** 11.5 (7.39-20.95) **Hospital** 33 (21-66)	**Intensive insulin (hours Median, range)** 132.2 (90-28)	**Conventional (hours Median, range,)** 228.2 (140-459)	**Intensive insulin** **Conventional** **# Hypoglycemic events (# of patients)** 1 (1) 8 (7)
16) Walters 2006	**Intensive insulin** NR	**Conventional** NR	**Intensive insulin** NR	**Conventional** NR	**Intensive insulin** **Conventional** **Serum Potassium [24 hr]** 4.0 ± 0.35 (mmol/L) 4.2 ± 0.41 mmol/L
17) de Azevedo 2007	**Intensive insulin** **ICU** 9 (4-22) **Hospital** 19.5 (7.7-39.2)	**Conventional** **ICU** 9 (4-15.5) **Hospital** 15.5 (4.2-21.7)	**Intensive insulin** NR	**Conventional** NR	**Intensive insulin** **Conventional** **Glascow Outcome Scale Extended** 9 (53) 5 (56) **Convulsions** 1 (3) 0
18) He, 2007∞	**TBD**	**TBD**	**TBD**	**TBD**	**TBD**
19) Bruno 2008	**Intensive insulin** NR	**Conventional** NR	**Intensive insulin** NR	**Conventional** NR	**Intensive insulin** **Conventional** **Patients with > 1 Hypoglycemia** 11 (35) 0 (0)
20) Mackenzie 2008	**Intensive insulin** **ICU (Hours Median)** 160 (66-461) **Hospital (Days Median)** 29 (15-58)	**Conventional** **ICU (Hours Median, range**) 167 (81-409**)** **Hospital (Days Median, range)** 27 (12-58)	**Intensive insulin (hours, Median, range)** 111 (24, 341)	**Conventional (hours, Median, range)** 120 (35, 330)	**Intensive insulin** **Conventional** **Incidence of hypoglycemia** **Morning laboratory** 8 (7) 1 (1) **Bedside** 50 (41) 9 (8)

Inclusion of studies to be re-assessed by panel members in Summer 2009

Study	LOS days		Ventilator days		Other
21) Oksanen 2007	NR	NR	NR	NR	**Intensive insulin** **Conventional** **% bl. gl measurements in targeted range** 71 (62-79) 47 (29-64)
22) He, 2008 ∞	**TBD**	**TBD**	**TBD**	**TBD**	**TBD**
23) Bilotta 2009	**ICU** 6 Median	**ICU** 8 Median	4.2 (median)	6.1 (median)	**Intensive Insulin** **Conventional** **# Pts ≥ 1 hypoglycemic episodes** 226 (93) 152 (63)
24) NICE SUGAR 2009	**ICU** 6 (2-11) **Hospital** 17 (8-35)	**ICU** 6 (2-11) **Hospital** 17 (8-35)	6.6 ± 6.6	6.6 ± 6.5	**Intensive insulin** **Conventional** **# Hypoglycemic severe events (# of patients)** 206/3016 (7) 15/3014 (1)
25) Zhang ∞	**TBD**	**TBD**	**TBD**	**TBD**	**TBD**

C.Random: concealed randomization ‡ refers to the # of patients with infections unless specified TNA: Total Nutrient Admixtures (-): median (range)
ITT: intent to treat; NA: not available ** RR= relative risk, CI= Confidence intervals ( ) : mean ± Standard deviation (number) NR: not reported

To convert values of glucose to mg/dL, multiply mmol/L X 18.01; to convert to mmol/L, multiply mg/dL x 0.05551
* data obtained from author
** data on group receiving pentastarch not shown
*** translated from Chinese
∞ articles to be translated from Chinese
Bilotta 2009 data replaces Bilotta 2007 and Bilotta 2008

Data on Length of Stay, Infections and Ventilation to be confirmed by panel members

Inclusion of studies to be re-assessed by panel members in Summer 2009

TOPIC: 10.4_ Intensive Insulin Therapy

Article inclusion log

Criteria for study selection

Type of study: RCT or Meta-analysis
Population: critically ill human patients (no elective sx.)
Intervention :TPN and /or EN
Outcomes: mortality, LOS, QOL, functional recovery, complications, cost. Exclude studies with only biochemical, metabolic or nutritional outcomes.

	Author	Journal	I	E	Why Rejected
1	Davies	Scot Med J 1991		√	Diabetic patients
2	Van den Berghe	NEJM 2001	√		
3	Stefanidis	Acta Cardiol 2002		√	Not ICU patients, Not mechanically ventilated
4	Van den Berghe	Crit Care Med 2003		√	Same study as NEJM 2001
5	Grey	Endocr Pract 2004	√		
6	Holzinger	Wien Klin Wochenschr 2004		√	No clinical outcomes
7	Lazar	Circulation 2004		√	Elective sx patients
8	Bland	Am J Crit Care 2005	√		
9	Henderson	American Thoracic Societ, 2005 [abstract]	√		
10	Hoedemaekers	Crit Care 2005		√	Elective surgery pts
11	Koskenkari	Ann Thorac Surg 2005		√	Insulin withdrawn within 6 hrs after admission to ICU
12	Mehta	JAMA 2005		√	Not ICU pts
13	Siroen	Crit Care Med 2005		√	Subset of earlier van Den Berg NEJM 2001 paper
14	Yu	Chin J Surg 2005	√		
15	Mitchell	Crit Care and Resuscitation 2006	√		
16	van Den Berghe	NEJM 2006	√		
17	van Wezel	J Clin Endocrinol & Metab 2006		√	Elective surgery pts
18	Walters	Cerebrovasc Dis 2006	√		
19	Wang	Chin Crit Care Med 2006	√		
20	Bilotta	J Neurosurg Anaesthesiol 2007		√	Included as Bilotta 2009
21	de Azevedo	Arq Neuropsiquiatr 2007	√		
22	Farah	IMAJ 2007	√		
23	Gray	Lancet Neurol 2007		√	Not intensive insulin therapy
24	He	Chinese Journal of Surgery [Zhongua Wai Ke Za Zhi 2007		√	Surgical ICU pts
25	Oksanen	Int Care Med 2007	√		
26	McMullin	J Crit Care 2007	√		
27	Arabi	Crit Care Med 2008	√		
28	Benito	Med Clin 2008		√	
29	Bilotta	Neurocrit Care 2008		√	Included as Bilotta 2009
30	Brunkhorst	NEJM 2008	√		
31	Bruno	Stroke 2008	√		
32	De La Rosa	Crit Care 2008	√		

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33	He 2008	Chinese Journal of Clinical Nutrition [Zhongguo linchuang yingyang zazhi] 2008	√		
34	Iapichino	Intensive Care Med 2008	√		
35	Mackenzie	Brit J Int Care 2008	√		
36	Bilotta	Anesthesiology 2009	√		
37	Devos	2008 [unpublished]	√		
38	Soylemez-Wiener	JAMA, 2008		√	Meta-analysis, individual studies looked at
39	NICE-SUGAR [Finfer]	NEJM, 2009	√		
40	Zhang	Chinese Journal of Clinical Nutrition 2008 [Zhongguo linchuang yingyang zazhi]	√		

I = included, E = excluded

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