



重症病患的血糖控制

Definition of Diabetes



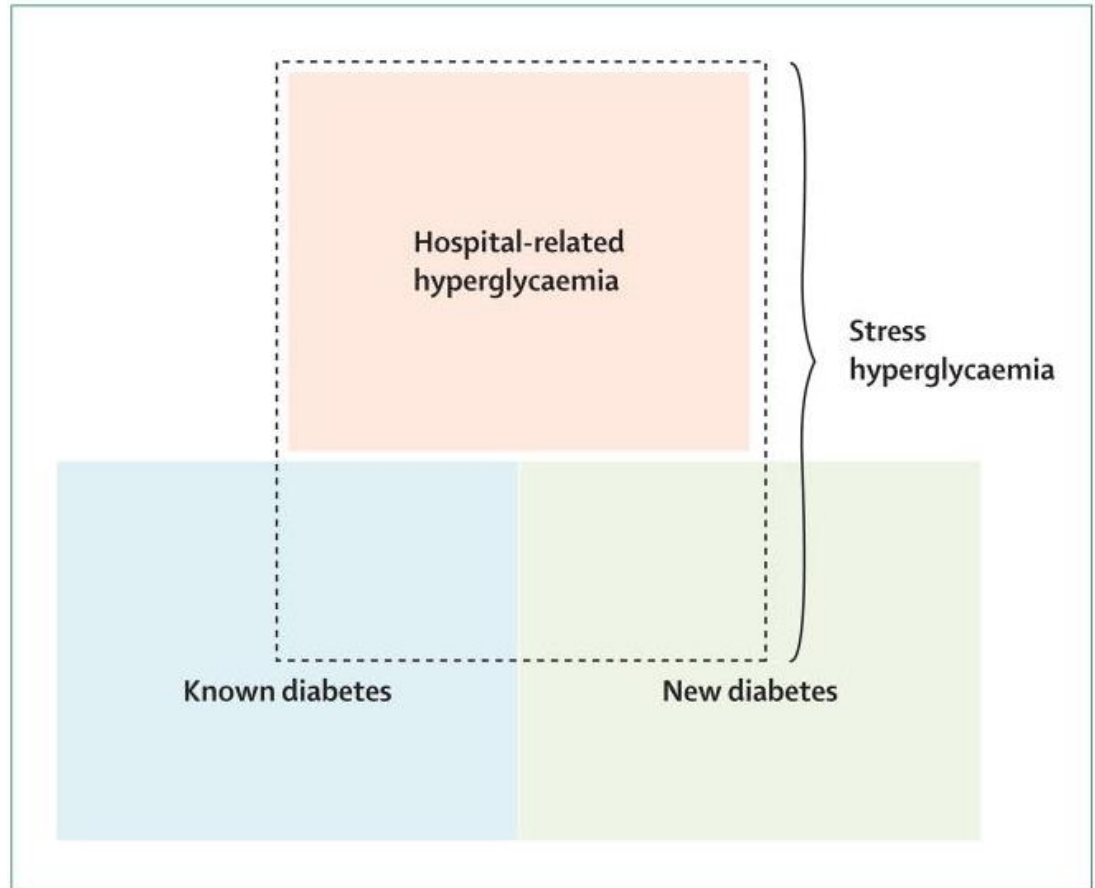
表二：糖尿病、糖尿病前期以及壓力高血糖症之定義

診斷	定義
糖尿病 (Diabetes mellitus)	空腹血糖值 ≥ 126 mg/dL 有高血糖症狀、以及隨機監測血糖值 ≥ 200 mg/dL 口服血糖耐受性測試 (75-g OGTT) 2 小時後血糖值 ≥ 200 mg/dL
空腹血糖異常 (Impaired fasting glucose)	空腹血糖值介於 100-125 mg/dL
葡萄糖耐受不良 (Impaired glucose tolerance)	口服血糖耐受性測試 (75-g OGTT) 2 小時後血糖值介於 140-199 mg/dL
壓力性高血糖症 (Stress induced hyperglycemia)	在住院期間被監測到空腹血糖值 ≥ 126 mg/dL, 或者隨機監測血糖值 ≥ 200 mg/dL, 但出院後就回復到正常值

壓力高血糖症 (Stress Hyperglycemia)



- Transient hyperglycemia
- Associated with critical illness



Factors Contributing to Hyperglycemia in critical illness



- Stress hormones (e.g., epinephrine and cortisol)
- Medications (glucocorticoids and catecholamines)
- Cytokines
- Impairing insulin-mediated glucose uptake by tissues
- Intravenous dextrose

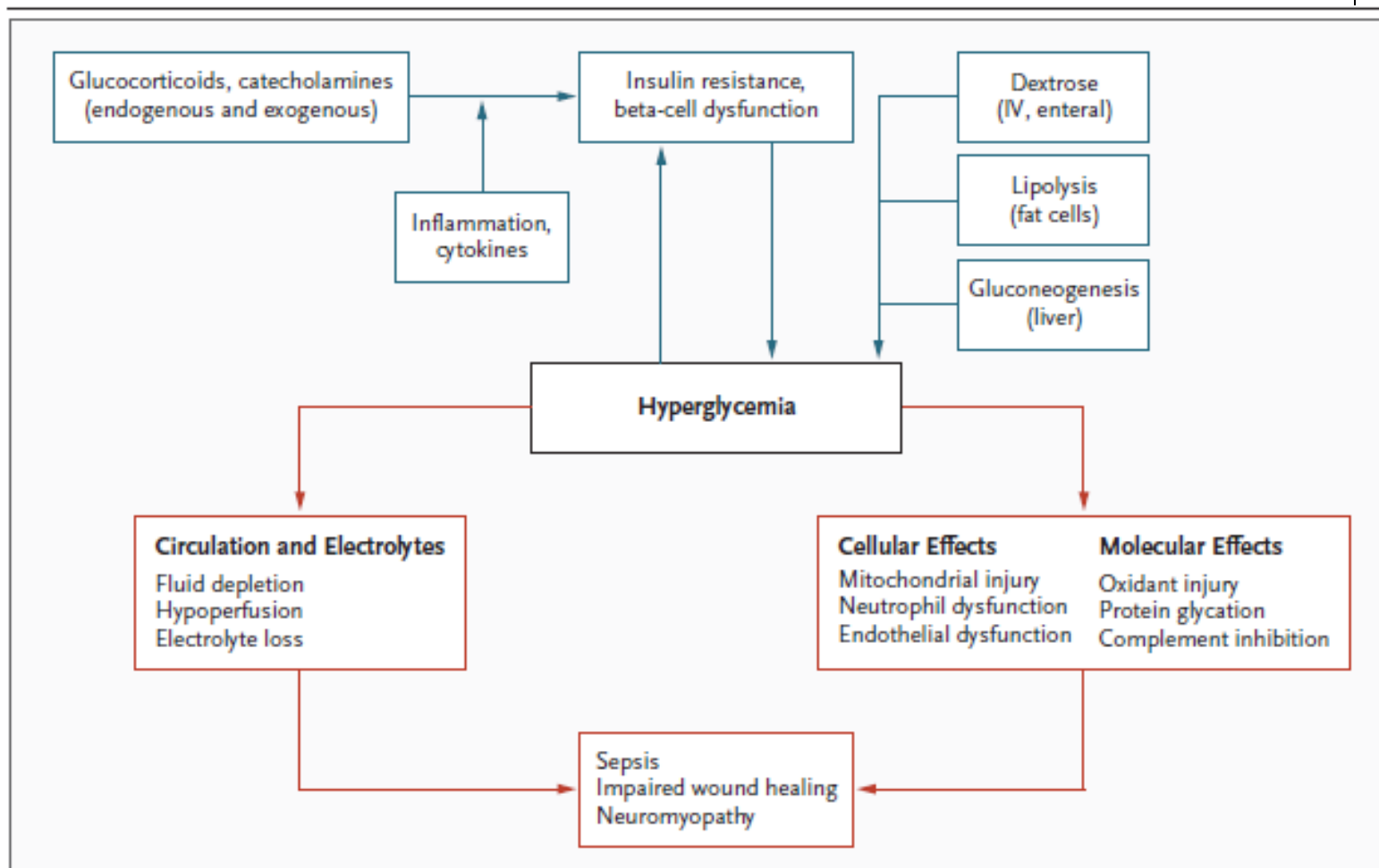


Figure 1. Causes and Effects of Stress Hyperglycemia.

Stress hyperglycemia can be caused by exogenous administration or endogenous production of glucose and by insulin resistance or reduced secretion of insulin owing to beta-cell dysfunction. The resulting hyperglycemia can potentiate insulin resistance. The consequences of elevated glucose levels may be manifested at the molecular or cellular level, combining to cause tissue abnormalities that include sepsis, impaired wound healing, and neuromyopathy. IV denotes intravenous.

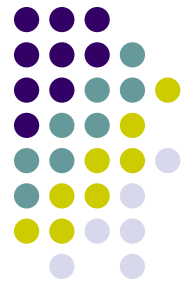


Effects of Hyperglycemia

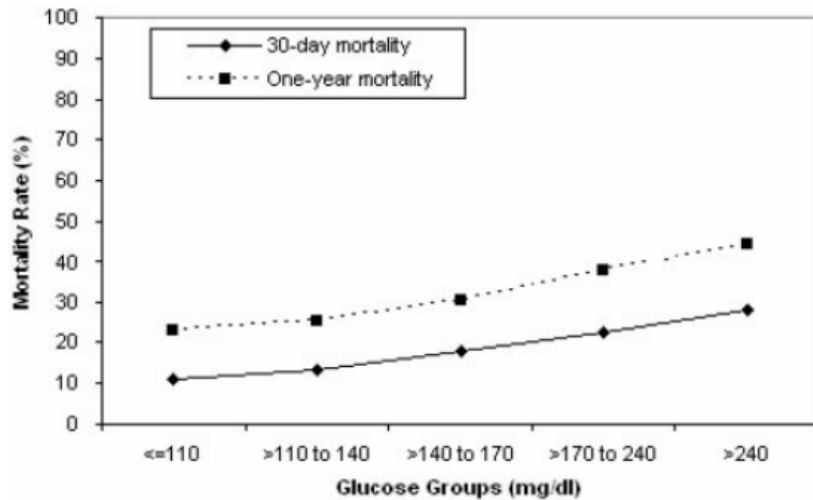
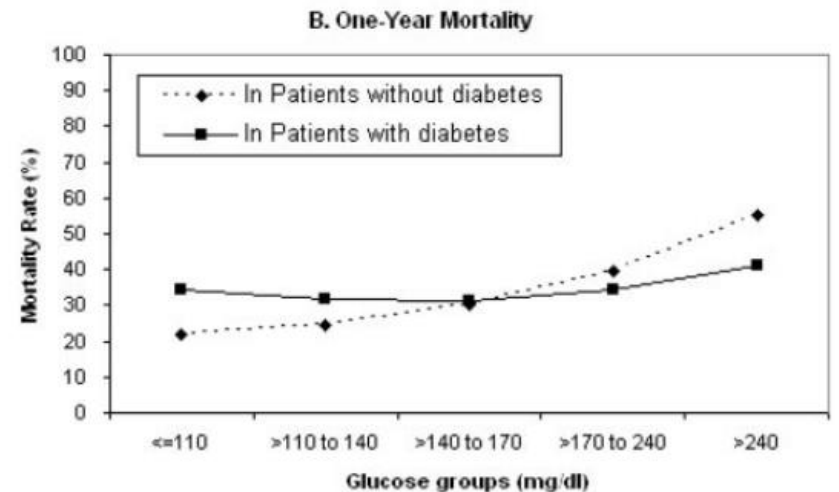
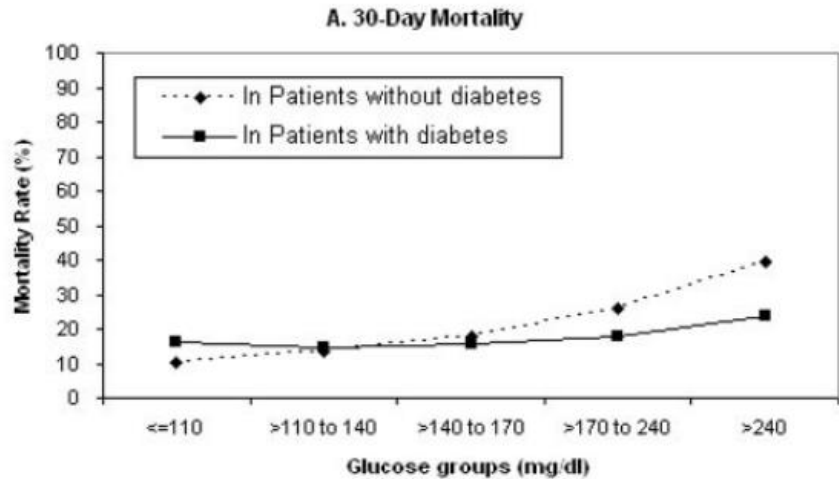
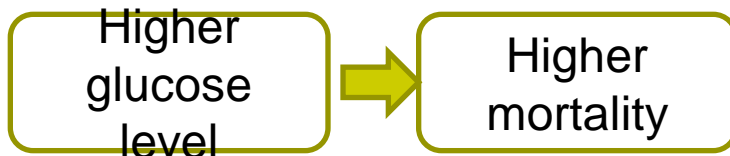
Poor outcome

High risk of mortality

Relationship Between Glucose and Mortality in AMI Pt



- Elderly and AMI pt



Relationship Between Glucose and Mortality in Stroke Pt



TABLE 1. Relative Risk of In-Hospital or 30-Day Mortality Associated With Stress Hyperglycemia in Patients With Stroke

Study	Stroke Subtype	Definition of Stress Hyperglycemia, mmol/L	% of Pts With Stress Hyperglycemia	No. of Events/Pts at Risk		Unadjusted Relative Risk (95% CI)
				In Pts With Stress Hyperglycemia	In Pts Without Stress Hyperglycemia	
Studies reporting data for nondiabetic patients						
Melamed ¹	TES, HS, SAH	>6.7 (fasting)§	35	58/108	36/205	3.06 (2.17–4.32)
Candelise ⁹	TES, HS	>6.1 (fasting)	38	18/23	11/38	2.70 (1.57–4.65)
Gray ¹²	TES, HS	≥8 (random)	14	7/13	16/77	2.59 (1.33–5.04)
Woo ^{23*}	TES, HS, LS	>7.8 (fasting)	13	17/23	38/156	3.03 (2.10–4.38)
Toni ^{25*}	TES	>6.7 (fasting)	36	21/93	15/164	2.47 (1.34–4.55)
Lee ³²	TES, HS, LS	≥7.0 (fasting)	30	5/16	1/38	11.88 (1.50–93.74)
Stig-Jørgensen ^{33*†}	TES, HS, LS	>6 (random)	61	81/382	22/241	2.32 (1.49–3.62)
Kiers ^{35*}	TES, HS, LS	>7.8 (fasting)	8	8/10	15/116	6.19 (3.52–10.88)
Cazzato ^{36*}	TES, LS	>6.1 (fasting)	63	15/37	2/22	4.46 (1.12–17.69)
Pooled relative risk						3.07 (2.50–3.79)

Acute hyperglycemia increased risk of in-hospital mortality after ischemic stroke in nondiabetic patients

Question 1



- What blood glucose goal do you suggest in adult critically ill patients?
 - Prevention of uncontrolled hyperglycemia is a desirable intervention

The New England Journal of Medicine



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VOLUME 345

NOVEMBER 8, 2001

NUMBER 19



INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

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- 1548 surgical ICU pts
- Conventional (BS 180-200) vs intensive (BS 80-110) insulin therapy

TABLE 3. MORTALITY.

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE*
Death during intensive care — no./total no. (%)	63/783 (8.0)	35/765 (4.6)	<0.04 (adjusted)
During first 5 days of intensive care	14/783 (1.8)	13/765 (1.7)	0.9
Among patients receiving intensive care for >5 days	49/243 (20.2)	22/208 (10.6)	0.005
Reason for intensive care			
Cardiac surgery	25/493 (5.1)	10/477 (2.1)	
Neurologic disease, cerebral trauma, or brain surgery	7/30 (23.3)	6/33 (18.2)	
Thoracic surgery, respiratory insufficiency, or both	10/56 (17.9)	5/66 (7.6)	
Abdominal surgery or peritonitis	9/58 (15.5)	6/45 (13.3)	
Vascular surgery	2/32 (6.2)	2/30 (6.7)	
Multiple trauma or severe burns	3/35 (8.6)	4/33 (12.1)	
Transplantation	1/44 (2.3)	2/46 (4.4)	
Other	6/35 (17.1)	0/35	
No history of diabetes	57/680 (8.4)	31/664 (4.7)	
No history of diabetes and >5 days of intensive care	45/218 (20.6)	20/187 (10.7)	
History of diabetes	6/103 (5.8)	4/101 (4.0)	
History of diabetes and >5 days of intensive care	4/25 (16.0)	2/21 (9.5)	
Cause of death — no.			0.02
Multiple-organ failure with proven septic focus	33	8	
Multiple-organ failure without detectable septic focus	18	14	
Severe brain damage	5	3	
Acute cardiovascular collapse	7	10	
In-hospital death — no./total no. (%)			
All patients	85/783 (10.9)	55/765 (7.2)	0.01
Patients receiving intensive care for >5 days	64/243 (26.3)	35/208 (16.8)	0.01

*P values were determined with the use of the chi-square test. For the primary outcome variable (death during intensive care), the P value has been corrected for the repeated interim analyses, according to the method of Lan and DeMets³⁰; the unadjusted P value is 0.005. Sequential interim analyses were not performed for the other variables, and nominal (unadjusted) P values are given for these comparisons.



INTENSIVE VERSUS CONVENTIONAL GLUCOSE CONTROL IN CRITICALLY ILL PATIENTS

THE **NICE-SUGAR** STUDY INVESTIGATORS

N ENGL J MED 360;13 NEJM.ORG MARCH 26, 2009

The NICE-SUGAR Study



Intensive glucose control :

81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter)

Conventional glucose control:

180 mg or less per deciliter (10.0 mmol or less per liter)

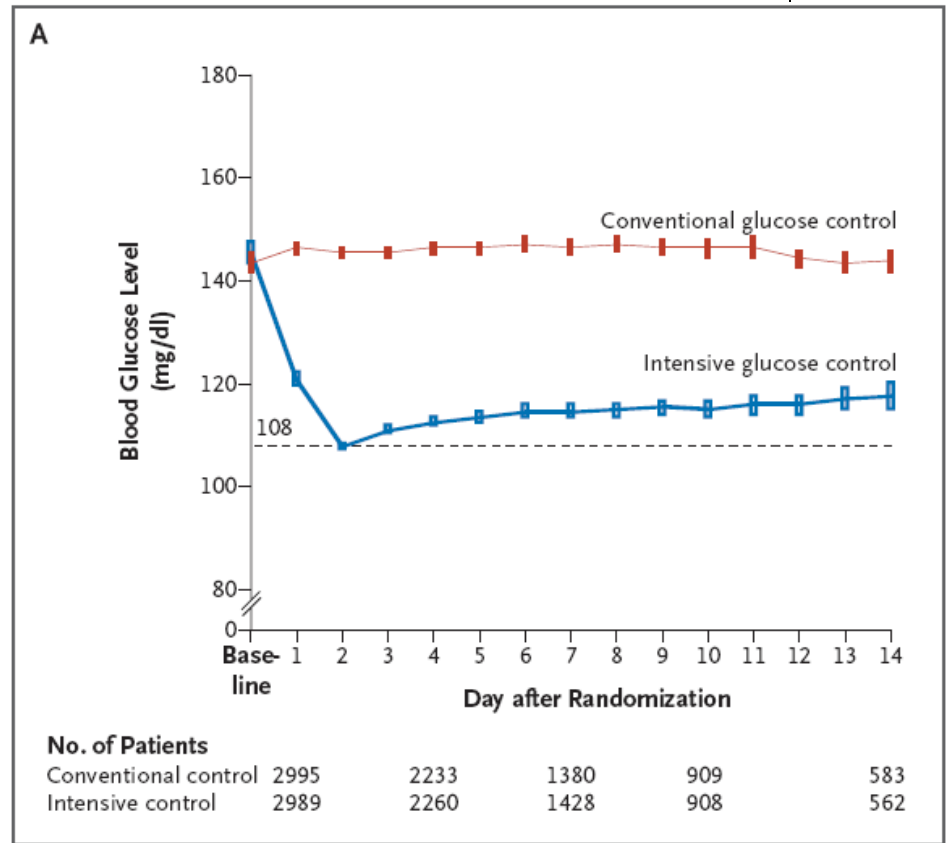


Table 3. Outcomes and Adverse Events.*

Outcome Measure	Intensive Glucose Control	Conventional Glucose Control	Odds Ratio or Absolute Difference (95% CI) [†]	Statistical Test	P Value
Death — no. of patients/total no. (%)				Logistic regression	
At day 90	829/3010 (27.5)	751/3012 (24.9)	1.14 (1.02 to 1.28)		0.02
At day 28	670/3010 (22.3)	627/3012 (20.8)	1.09 (0.96 to 1.23)		0.17
Potentially life-sustaining treatment limited or withheld before death — no. of patients/total no. (%)	746/816 (91.4)	669/741 (90.3)	1.15 (0.81 to 1.62)	Logistic regression	0.44
Limited because death was imminent	527/816 (64.6)	459/741 (61.9)	1.12 (0.91 to 1.38)		0.28
Withheld because not appropriate	219/816 (26.8)	210/741 (28.3)	0.93 (0.74 to 1.16)		0.51
CPR as terminal event — no. of patients/total no. (%)	70/816 (8.6)	72/741 (9.7)	0.87 (0.62 to 1.23)	Logistic regression	0.44
Days from randomization to limitation or withholding of potentially life-sustaining treatment — median (IQR)	6 (3 to 16)	6 (2 to 15)		t-test	0.42
Proximate cause of death — no. of patients/total no. (%)				Pearson's test	0.12
Cardiovascular-distributive shock	168/829 (20.3)	140/751 (18.6)			
Other	113/829 (13.6)	111/751 (14.8)			
Place of death — no. of patients/total no. (%)					
ICU	546/829 (65.9)	498/751 (66.3)			
Elsewhere in hospital	220/829 (26.5)	197/751 (26.2)			
Outside hospital, after discharge	63/829 (7.6)	56/751 (7.5)			
Severe hypoglycemia — no. of patients/total no. (%)	206/3016 (6.8)	15/3014 (0.5)	14.7 (9.0 to 25.9)	Logistic regression	<0.001
Days in ICU — median (IQR)	6 (2 to 11)	6 (2 to 11)	0	Log-rank test	0.84
Days in hospital — median (IQR)	17 (8 to 35)	17 (8 to 35)	0	Log-rank test	0.86

Significantly increased risk of severe hypoglycemia and 90-days mortality rate in intensive glucose control group

Different Setting in ICU Patients



Table 2 Results of subgroup analysis

Outcome	Subgroup	Odds ratio of network analysis (95 % confidential interval)					
		-110 vs 110-144	-110 vs 144-180	-110 vs 180-	110-144 vs 144-180	110-144 vs 180-	144-180 vs 180-
Mortality	Over all	1.10 (0.67-1.7)	1.10 (0.89-1.27)	0.90 (0.75-1.08)	1.0 (0.60-1.6)	0.83 (0.53-1.28)	0.82 (0.65-1.1)
	Surgical ICU	1.32 (0.15-6.8)	1.12 (0.32-2.56)	0.83 (0.23-1.81)	0.94 (0.12-7.7)	0.67 (0.13-3.45)	0.72 (0.19-2.63)
	Medical ICU	1.00 (0.61-1.70)	1.05 (0.84-1.33)	0.90 (0.72-1.16)	1.03 (0.60-1.85)	0.87 (0.53-1.54)	0.85 (0.63-1.20)
	Non-diabetic patient >50 %	1.6 (0.80-3.3)	1.0 (0.77-1.3)	0.92 (0.75-1.2)	0.65 (0.30-1.3)	0.57 (0.29-1.1)	0.88 (0.65-1.3)
	Mortality >20 %	1.1 (0.63-2)	1.1 (0.92-1.3)	0.94 (0.79-1.1)	0.96 (0.53-1.8)	0.83 (0.48-1.5)	0.87 (0.68-1.1)
	Actual mean glycemic level	0.74 (0.50-1.3)	0.75 (0.51-1.2)	0.43 (0.19-1.2)	1.0 (0.84-1.1)	0.59 (0.27-1.4)	0.58 (0.26-1.4)
Infection	Over all	1.30 (0.71-2.40)	1.11 (0.77-1.79)	0.77 (0.53-1.16)	0.91 (0.45-1.72)	0.63 (0.38-1.00)	0.71 (0.38-1.20)
	Surgical ICU	1.20 (0.29-5.30)	0.81 (0.16-3.84)	0.67 (0.23-2.13)	0.69 (0.07-5.40)	0.58 (0.23-1.39)	0.83 (0.13-6.60)
	Medical ICU	1.30 (0.58-2.90)	1.11 (0.83-1.85)	0.95 (0.64-1.48)	0.90 (0.40-2.08)	0.75 (0.33-1.61)	0.85 (0.43-1.40)
	Non-diabetic patient >50 %	1.30 (0.67-2.6)	1.09 (0.68-2.1)	0.79 (0.51-1.2)	0.88 (0.40-2.00)	0.61 (0.34-1.09)	0.70 (0.34-1.09)
	Mortality >20 %	1.3 (0.65-2.5)	1.1 (0.72-1.8)	0.94 (0.58-1.4)	0.84 (0.42-1.9)	0.71 (0.41-1.3)	0.85 (0.43-1.5)
	Actual mean glycemic level	0.65 (0.37-1.33)	0.61 (0.36-1.16)	0.18 (0.008-1.9)	0.95 (0.66-1.28)	0.27 (0.012-2.56)	0.28 (0.013-2.9)
Hypoglycemia	Over all	0.80 (0.22-2.70)	4.34 (2.4-8.3)	7.5 (4.4-13)	5.4 (1.6-19)	9.3 (2.8-34)	1.77 (0.77-3.70)
	Surgical ICU	0.48 (0.007-20)	5.88 (1.67-180)	6.7 (1.5-39)	14.0 (0.42-3500)	14 (0.56-780)	1.2 (0.03-7)
	Medical ICU	0.83 (0.13-4.30)	4.35 (1.54-11.4)	7.69 (3.45-17.2)	5.26 (1.09-29.4)	9.09 (1.82-62.5)	1.80 (0.53-6.3)
	Non-diabetic patient >50 %	1.0 (0.26-4.0)	5.0 (2.4-11.0)	7.2 (4.0-13.0)	4.9 (1.3-20)	7.0 (1.8-29)	1.4 (0.56-3.6)
	Mortality >20 %	0.83 (0.21-3.0)	4.0 (2.1-7.7)	7.1 (3.9-13)	4.8 (1.4-19)	8.5 (2.3-35)	1.8 (0.74-4.1)
	Actual mean glycemic level	1.2 (0.36-4.2)	7.4 (2.3-25)	8.3 (0.62-370)	6.3 (3.9-10)	6.8 (0.69-270)	1.1 (0.10-45)

Bold indicates that there is a significant difference

Table 1. Guidelines from Professional Organizations on the Management of Glucose Levels in the ICU.*

Year	Organization	Patient Population	Treatment Threshold	Target Glucose Level <i>mg/dl</i>	Definition of Hypoglycemia	Updated since NICE-SUGAR Trial, 2009†
2009	American Association of Clinical Endocrinologists and American Diabetes Association	ICU patients	180	140–180	<70	Yes
2009	Surviving Sepsis Campaign	ICU patients	180	150	Not stated	Yes
2009	Institute for Healthcare Improvement	ICU patients	180	<180	<40	Yes
2008	American Heart Association	ICU patients with acute coronary syndromes	180	90–140	Not stated	No
2007	European Society of Cardiology and European Association for the Study of Diabetes	ICU patients with cardiac disorders	Not stated	“Strict”‡	Not stated	No

* The guidelines from the organizations listed are available online: American Association of Clinical Endocrinologists and American Diabetes Association, www.aace.com/pub/pdf/guidelines/InpatientGlycemicControlConsensusStatement.pdf; Surviving Sepsis Campaign, www.survivingsepsis.org/About_the_Campaign/Documents/SSC%20Statement%20on%20Glucose%20Control%20in%20Severe%20Sepsis.pdf; Institute for Healthcare Improvement, www.ihl.org/IHI/Topics/CriticalCare/IntensiveCare/Changes/ImplementEffectiveGlucoseControl.htm; American Heart Association, <http://circ.ahajournals.org/cgi/content/short/117/12/1610>; and European Society of Cardiology and European Association for the Study of Diabetes, www.easd.org/easdwebfiles/homepage/escandeadsdguidelines.pdf.

† The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial is reported by Finfer et al.¹³

‡ The guideline recommends “strict blood glucose control with intensive insulin therapy” and refers to studies in which such therapy has target glucose levels of 80 to 110 mg per deciliter (4.4 to 6.1 mmol per liter).

Guideline Suggestion For Management of Glucose in Sepsis Pt



Q. Glucose Control

1. A protocolized approach to blood glucose management in ICU patients with severe sepsis commencing insulin dosing when 2 consecutive blood glucose levels are >180 mg/dL. This protocolized approach should target an upper blood glucose ≤ 180 mg/dL rather than an upper target blood glucose ≤ 110 mg/dL (grade 1A).
2. Blood glucose values be monitored every 1–2 hrs until glucose values and insulin infusion rates are stable and then every 4 hrs thereafter (grade 1C).
3. Glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may not accurately estimate arterial blood or plasma glucose values (UG).

Glycemic Target in ICU Settings- Suggestion From ADA Guideline



- Initiate insulin starting at ≤ 180 mg/dL (10.0 mmol/L)
- Once insulin is started, a target glucose range of 140-180 mg/dL (7.8-10.0 mmol/L) is recommended for most patients
 - More stringent goals (110–140mg/dL) may be appropriate for select patients

Discussion



- What blood glucose goal do you suggest in adult critically ill patients?
 - Initiate insulin starting at ≤ 180 mg/dL
 - Target glucose range of 140-180 mg/dL

Question 2



- What treatment options are available for achieving optimal glycemic targets in the critical care units?

The NICE-SUGAR Study

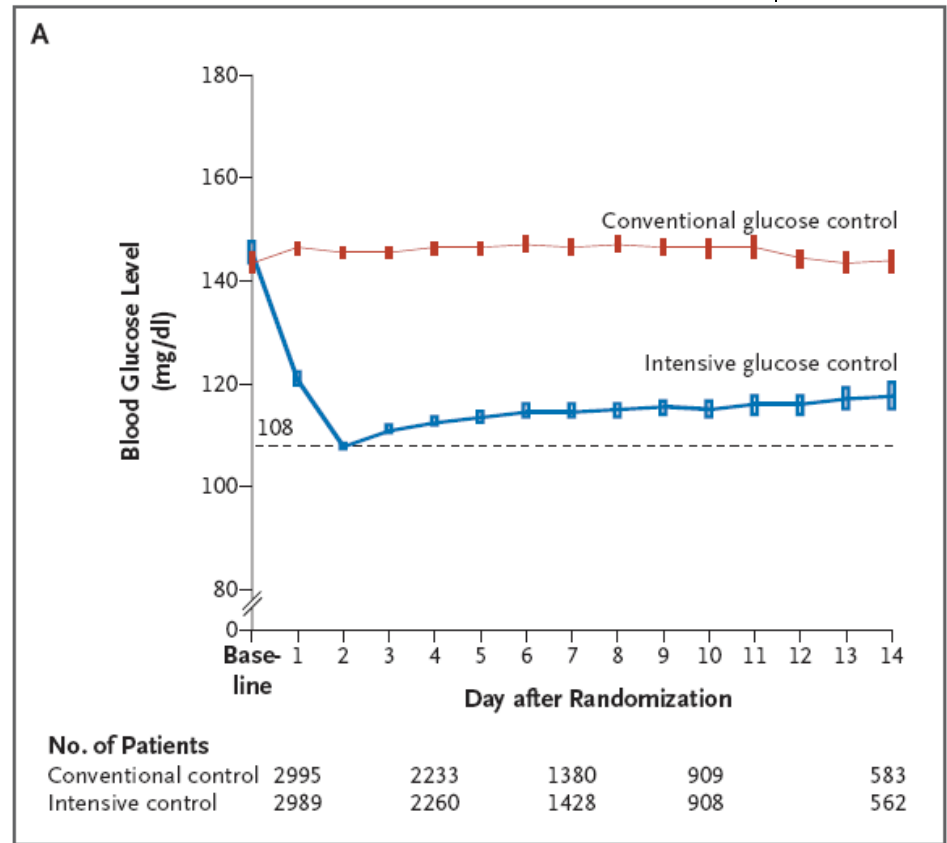


Intensive glucose control :

81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter)

Conventional glucose control:

180 mg or less per deciliter (10.0 mmol or less per liter)



Intravenous infusion of insulin in saline is used to control blood sugar

IV Insulin Infusion



- Continuous **IV insulin infusion** is **the most effective method** to achieving specific glycemic targets in the critical care setting.
 - Short half-life of circulating insulin
 - Rapid dosing adjustments

Choice of Insulin Analog



表 4-3. 胰島素的種類及其作用時間

胰島素製劑	發揮效力時間	高峰時間	全程作用時間
超短效胰島素			
Lispro	5-15 分	1-2 小時	4-6 小時
Aspart	5-15 分	1-2 小時	4-6 小時
短效胰島素			
Human regular	30-60 分	2-4 小時	6-10 小時
中效胰島素			
Human NPH	1-2 小時	4-8 小時	10-20 小時
Lente	1-2 小時	4-8 小時	10-20 小時
長效胰島素			
Ultralente	2-4 小時	無法預測	16-20 小時
超長效胰島素			
Glargine	1-2 小時	穩定無高峰期	24 小時

IV, SC

Other Situation



- Outside the ICU:
 - Insulin is still preferred in hospital setting
 - IV insulin infusions will usually require transition to SC administered insulin when they begin eating regular meals or are transferred to lower-intensity care.
 - SC administered insulin must be given 1-4 h before discontinuation of IV insulin therapy in order to prevent hyperglycemia.

Other Situation



- Considering nutrition support

Table 13.1—Insulin dosing for enteral/parenteral feedings

Situation	Basal	Bolus
Continuous enteral feedings	Glargine q.d. or NPH/detemir b.i.d.	SQ rapid-acting correction every 4 h
Bolus enteral feedings	Continue prior basal; if none, consider 10 units NPH or glargine insulin	SQ rapid-acting insulin with each bolus feeding to cover the bolus feeding and to correct for hyperglycemia
Parenteral feedings	Regular insulin to TPN IV bottle	Rapid-acting insulin SQ every 4 h to correct for hyperglycemia

IV, intravenous; SQ, subcutaneous; TPN, total parenteral nutrition.

Discussion



- What treatment options are available for achieving optimal glycemic targets in the critical care units?
 - Insulin infusion therapy
 - Other short-acting analog may also be considered

Question



- What is the risk factor of hypoglycemia in the ICU population?

Risk Factors For Hypoglycemia



- Renal failure
- Interruption of caloric intake
- Sepsis with the use of vasoactive infusions,
- Insulin therapy
- CRRT with a bicarbonate-based replacement fluid .
- Other underline disease
 - Liver disease
 - immune compromise

Discussion



- Considering the risk factor of hypoglycemia in the ICU population
 - Different target glucose range may be considered

Restricted glycemic control may be considered	Higher glucose ranges may be acceptable
Cardiac surgery Acute ischemic cardiac Neurological events	Terminally ill Severe comorbidities Frequent glucose monitoring or close nursing supervision is not feasible

Question



- How should insulin-induced hypoglycemia be treated in ICU patients?

Suggestion From ADA Guideline 2016



- A hypoglycemia management protocol should be established for each patient:
 - A plan for prevention and treatment of hypoglycemia should be developed
 - All episodes of hypoglycemia should be documented and tracked
 - The treatment plan should be reviewed and changed when glucose is <70 mg/dL (3.9 mmol/L)

Hypoglycemia in ICU Pt



- Stop the insulin infusion
- Administering 10–20g of hypertonic(50%) dextrose.
 - ✓ 50% dextrose dose in grams = $[100 - \text{BG}] \times 0.2 \text{ g}$
- The BG should be repeated in 15 mins with further dextrose administration as needed to achieve BG > 70 mg/dL with a goal to avoid iatrogenic hyperglycemia.

Question



- How often should BG be monitored in ICU patients?

Monitoring Blood Sugar



- BG be monitored **every 1–2 hrs** for most patients receiving an insulin infusion.
- **Every 4 hrs** based on the stability of the BG values within the desired range, as well as an assessment of patient clinical stability.
- **Unstable patients** should have BG monitored at least **every hour** to allow rapid recognition of BG outside the goal range

Hyperglycemia Bundle in TMUH



# Hyperglycemia Bundle	0	CONT.	
RI4U(血糖>150),8U(血糖>200),12U(血糖>250),16U(血糖>300)		CONT.	
若由進食突然改NPO則RI劑量減半,11pmRI劑量減半,血糖<200不		CONT.	
血糖>300一天兩次立即使用RI infusion protocol,需醫師訂		CONT.	RI4U(血糖>150),8U(血糖>200),12U(血糖>250),16U(血糖>300)SQ

Take Home Message



- Glucose targeting for most ICU pts: 140-180 mg/dL
- Insulin is the preferred method
- Close monitor blood sugar to prevent hypoglycemia



Thank You!