# Enteral and parenteral nutrition – *critically ill patients*

*In behalf of the EN*

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ROSPEN Romanian Society of Parenteral and Enteral Nutrition
Societatea Română de Nutriţie Parenterală şi Enterală

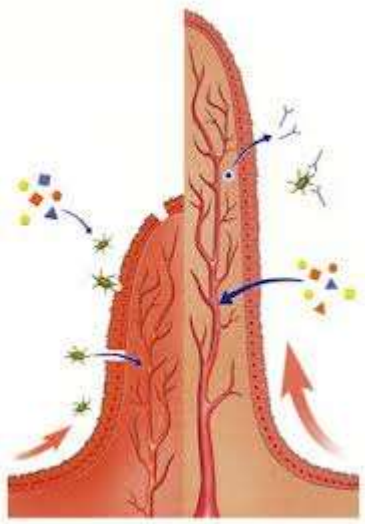
UNIVERSITAS MEDICINAE ET PHARMACIAE "CAROLUS DAVILA" - BUCUREŞTIS
DOCENDO DISCITUR
A.D. 1857

# Nutrition of Intestinal Mucosa

| | Luminal Nutrition | Main Substrates |
|---|---|---|
| Small Bowel | 30% | Glutamin |
| Colon | 80% | SCFA‘s |

# Lack of endoluminal substrates

- ↑intestinal permeability
- ↓villous height ⇒ malabsorption, an impaired ability to act as a barrier (endogenous bacteria and toxins)



# Lack of endoluminal substrates

- Intestinal epithelial cell apoptosis, villi- and crypt atrophy during PN, **even if** energy requirements are **covered by 100%**
- Supports the concept that rather lack of endoluminal substrates than TPN *per se* is responsible for many of the adverse events seen in patients fed with TPN

*Sun X et al. JPEN J Parenter Enteral Nutr. 2006;30:474-9*

# EN

- ↓stress ulcer
- ↑intestinal peristalsis
- ↓risk of colonization
- ↑hormonal intestinal function

# TPN

- Reduction of lymphotoxin-β-receptor expression **by TPN**
- Evidence that **TPN** *per se* (not only lack of EN) **impairs GALT and mucosal immunity**

*Kang W et al. Ann Surg. 2006;244:392-399*

# Failure of Enteral Nutrition

- **Immunological alterations and impairment of “gut associated lymphatic tissue” (GALT)**
  - Bowel becomes source of activated cells and pro-inflammatory stimuli during “gut starvation”
  - Secondary changes in permeability and maybe bacterial translocation challenge GALT

*Kudsk KA. Am J Surg 2003;185:16–21*

# Positive Effects of EN

- IgA-levels and number of circulating lyphocytes  of GALT are positively influenced by EN
  - Lymphocytes migrate in non-intestinal tissue (i.e. lung) and modify immune response
  - Neuroendocrine system-/bacteria-host-interaction of the gut influences regulation of inflammation also outside of the GI tract

*Kudsk KA, Am J Surg 2002, 183:390-393*
*Luyer MD, et al. J Exp Med 2005, 202:1023-1029*

# Message 1

- EN if ever possible
- (T)PN only if EN not possible or insufficient

# EN contraindications

- Absolut CI
  - Immediate postoperatively or after trauma
  - Shock status (severe acidosis)
  - Severe hypoxia
- Relative CI
  - Dynamic ileus
  - Severe vomiting
  - High quantity of gastric aspirate (> 1200 ml/24h)
  - Severe diarrhea
  - Abdominal hypertension
  - Abdominal dysfunction

# EN contraindications

- But TPN is permitted

- Mesenteric ischemia
- Mechanical ileus
- Acute abdominal pain
- Abdominal compartment syndrome

# Timing of EN

Metaanalysis of 6 RCT ‘s with 234 patients


Chiarelli A, Enzi G, Casadei A, et al. Very early nutrition supplementation in burned patients. Am J Clin Nutr. 1990;51:1035–1039

Chuntrasakul C, Chinswangwatanakul V, Chockvivatanavanit S. Early nutritional support in severe traumatic patients. J Med Assoc Thai. 1996;79:21–25 Pupelis G, Selga G, Austrums E, Kaminski A. Jejunal feeding, even when instituted late, improves outcomes in patients with severe pancreatitis and peritonitis. Nutrition. 2001;17:91–94. doi: 10.1016/S0899-9007(00)00508-6

Kompan L, Kremzar B, Gadzijev E, Prosck M. Effects of early enteral nutrition on intestinal permeability and the development of multiple organ failure after multiple injury. Intensive Care Med. 1999;25:157–161. doi: 10.1007/s001340050809]

Pupelis G, Austrums E, Jansone A, Sprucs R, Wehbi H. Randomised trial of safety and efficacy of postoperative enteral feeding in patients with severe pancreatitis: preliminary report. Eur J Surg. 2000;166:383–387. doi: 10.1080/11024150075000893

Kompan L, Vidmar G, Spindler-Vesel A, Pecar J. Is early enteral nutrition a risk factor for gastric intolerance and pneumonia? Clin Nutr. 2004;23:527–532. doi: 10.1016/j.clnu.2003.09.013

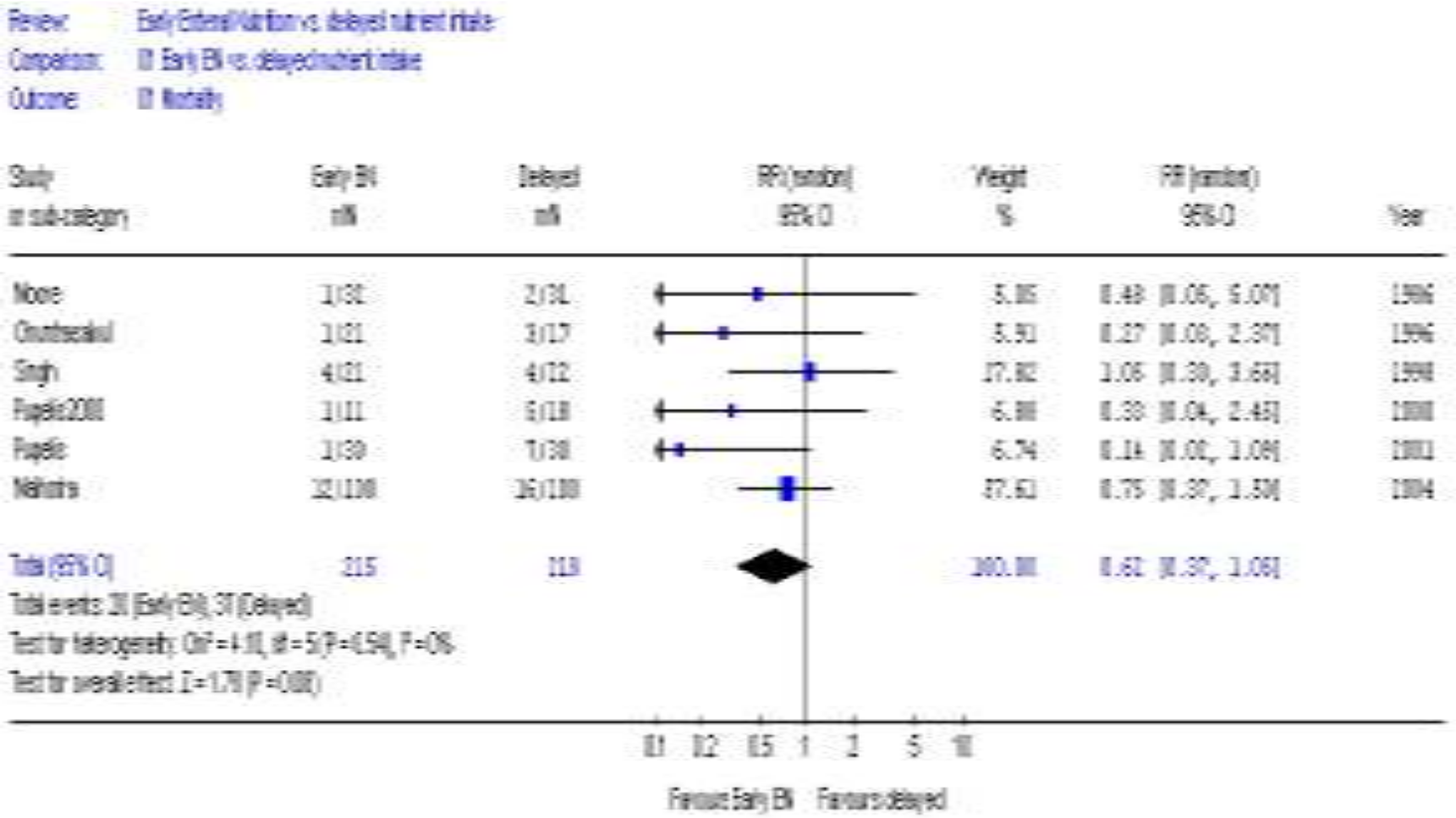

*Doig GS, et al. Intensive Care Med. 2009;35:2018–2027*

# Timing of EN

- Start with EN < 24 h vs > 24 h
  - Results
    - Significant reduction in mortality (OR 0.34, 95% CI 0.14-0.85) and incidence in pneumonias (OR 0.31, CI 0.12-0.78)

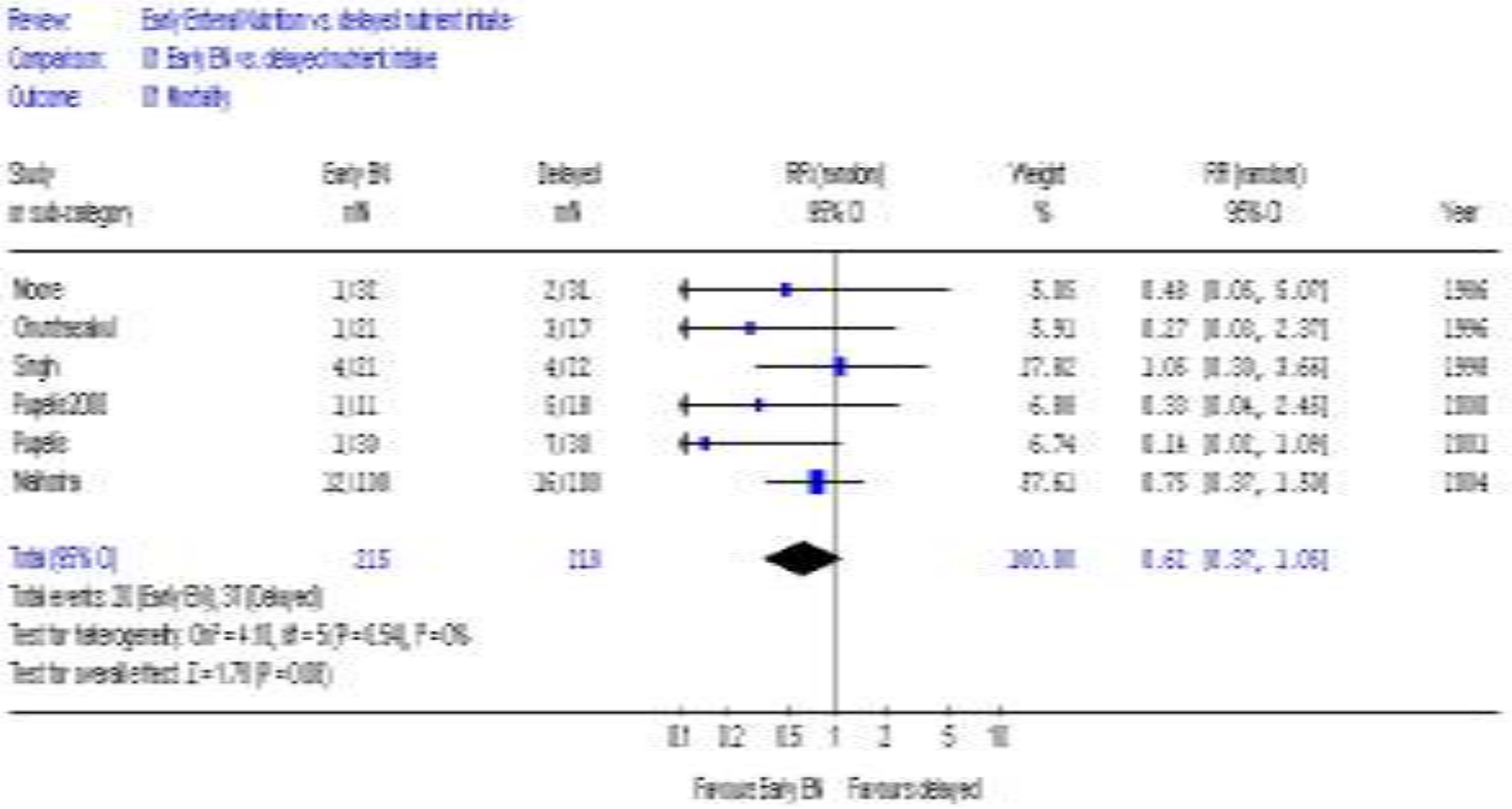
*Doig GS, et al. Intensive Care Med. 2009;35:2018–2027*

# Early vs. Late EN: Mortality



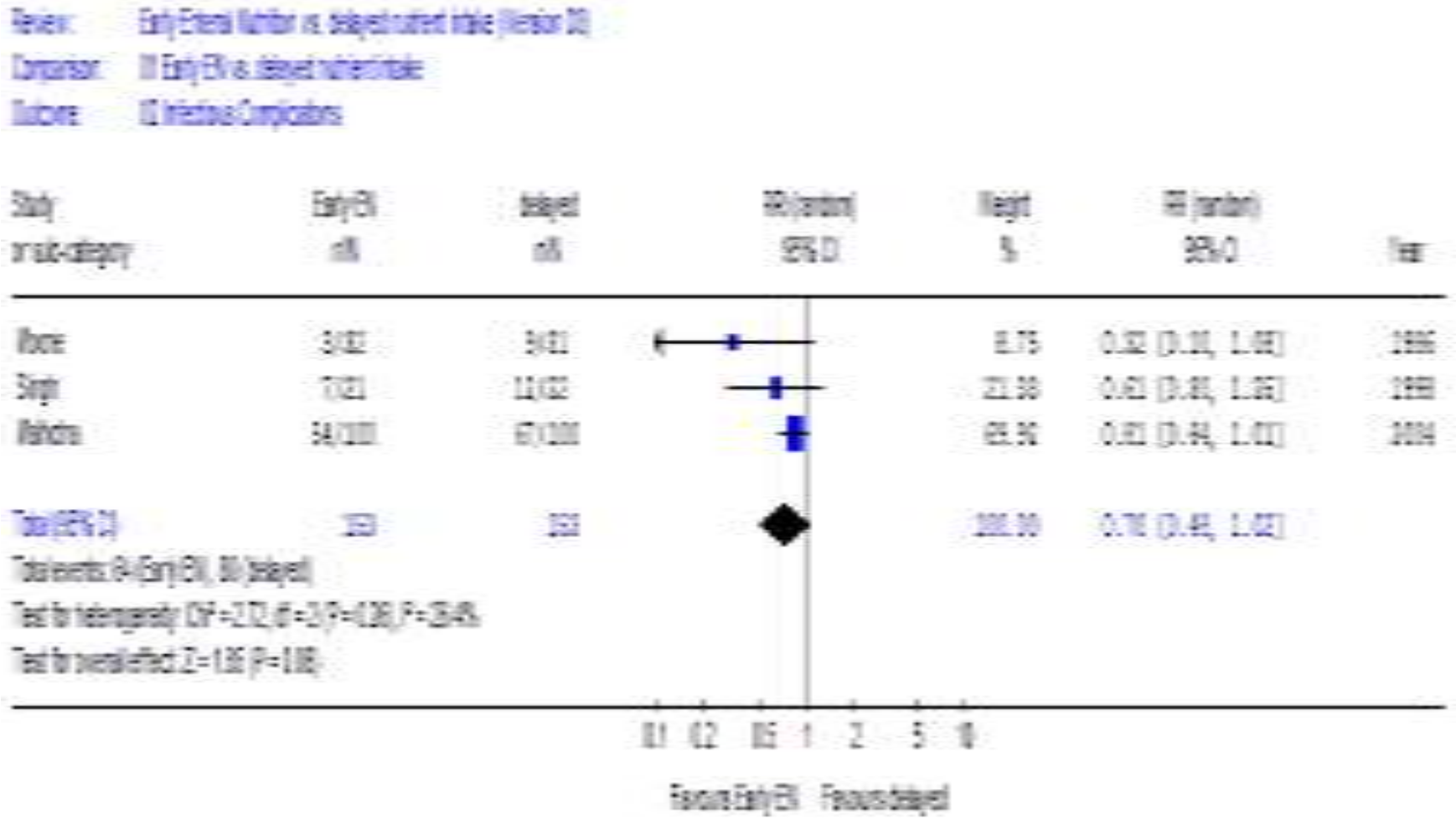
*Doig GS, et al. Intensive Care Med. 2009;35:2018–2027*

# Early EN vs. i.v. fluid/no EN: Mortality



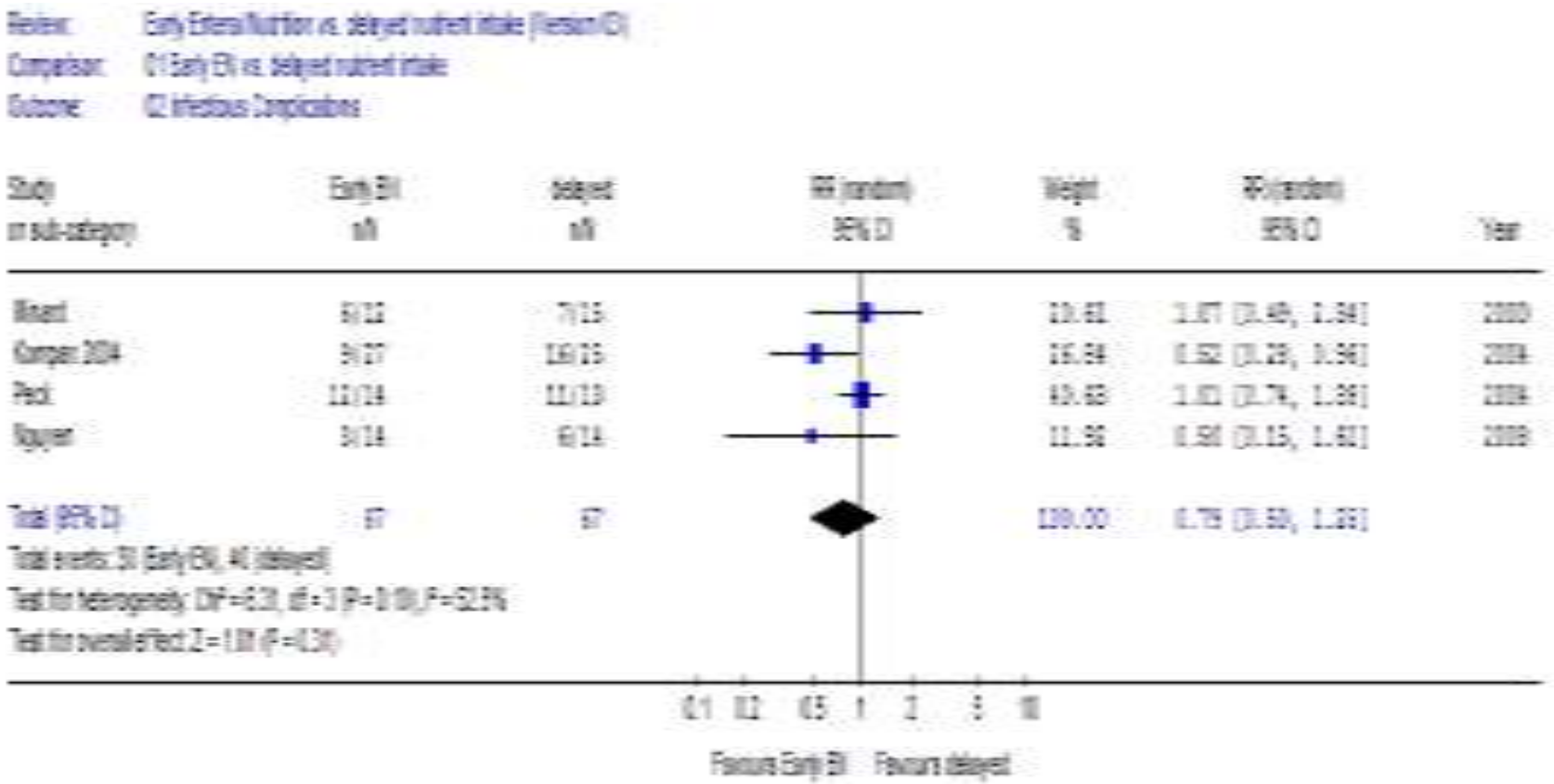
*Doig GS, et al. Intensive Care Med. 2009;35:2018–2027*

# Early EN vs. i.v. Fluid /no EN: Infectious Complications



*Doig GS, et al. Intensive Care Med. 2009;35:2018–2027*

# Earl vs. Late EN: Infectious Complications



***No influence on: Ventilator days, LOICUS, LOHS***

*Doig GS, et al. Intensive Care Med. 2009;35:2018–2027*

# Message 2: Early vs. Late EN

The problem with randomised studies in all the nutritional literature is the lack of a proper methodology leading to a high risk of bias => over estimation of treatment effects

Despite of that:

Repetitive frequent findings of **beneficial effects of early EN (< 24h)**

# EN complications

- Abdominal distension
- Diarrhea
- Intestinal necrosis (intrajejunal feeding)
- Tracheal aspiration
- Mechanical complication

# Timing of PN

- Patients who can be fed adequately within the first 3 days do not need PN
- Malnourished patients with partial GI intolerance profit from pre- and earlier (> 24-36 h) supplementing PN
- Patients with prolonged (partial) GI-intolerance profit from PN supplementation
  - Not immediately after the admission
  - If ever possible, a minimum of enteral (immuno-) nutrition should be given

# EN vs EN+PN: Systematic Review

- 5 studies; in all studies EN and PN were started simultaneously
  - No significant effect on mortality by combining EN + PN
  - No effect on infectious complications, LOHS, ventilator days

CONCLUSION: In critically ill patients without malnutrition und with working GI tract simultaneous start of EN and PN is useless compared to EN alone

*Dhaliwal R et al. Intensive Care Med. 2004; 30:1666-71*

Clinical Nutrition 28 (2009) 387–400

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journal homepage: http://www.elsevier.com/locate/clnu

# ESPEN Guidelines on Parenteral Nutrition: Intensive care

Pierre Singer[a], Mette M. Berger[b], Greet Van den Berghe[c], Gianni Biolo[d], Philip Calder[e], Alastair Forbes[f], Richard Griffiths[g], Georg Kreyman[h], Xavier Leverve[i], Claude Pichard[j]

- All patients who are not expected to be on normal nutrition within 3 days should receive PN within 24–48 h if EN is contraindicated or if they cannot tolerate EN. (Grade C)
- In the absence of indirect calorimetry, ICU patients should receive 25 kcal/kg/day increasing to target over the next 2–3 days (Grade C)
- All patients receiving less than their targeted enteral feeding after 2 days should be considered for supplementary PN (Grade C)

# PN complications

- Mechanical
- Infectious
- Metabolic

# Insulin resistance

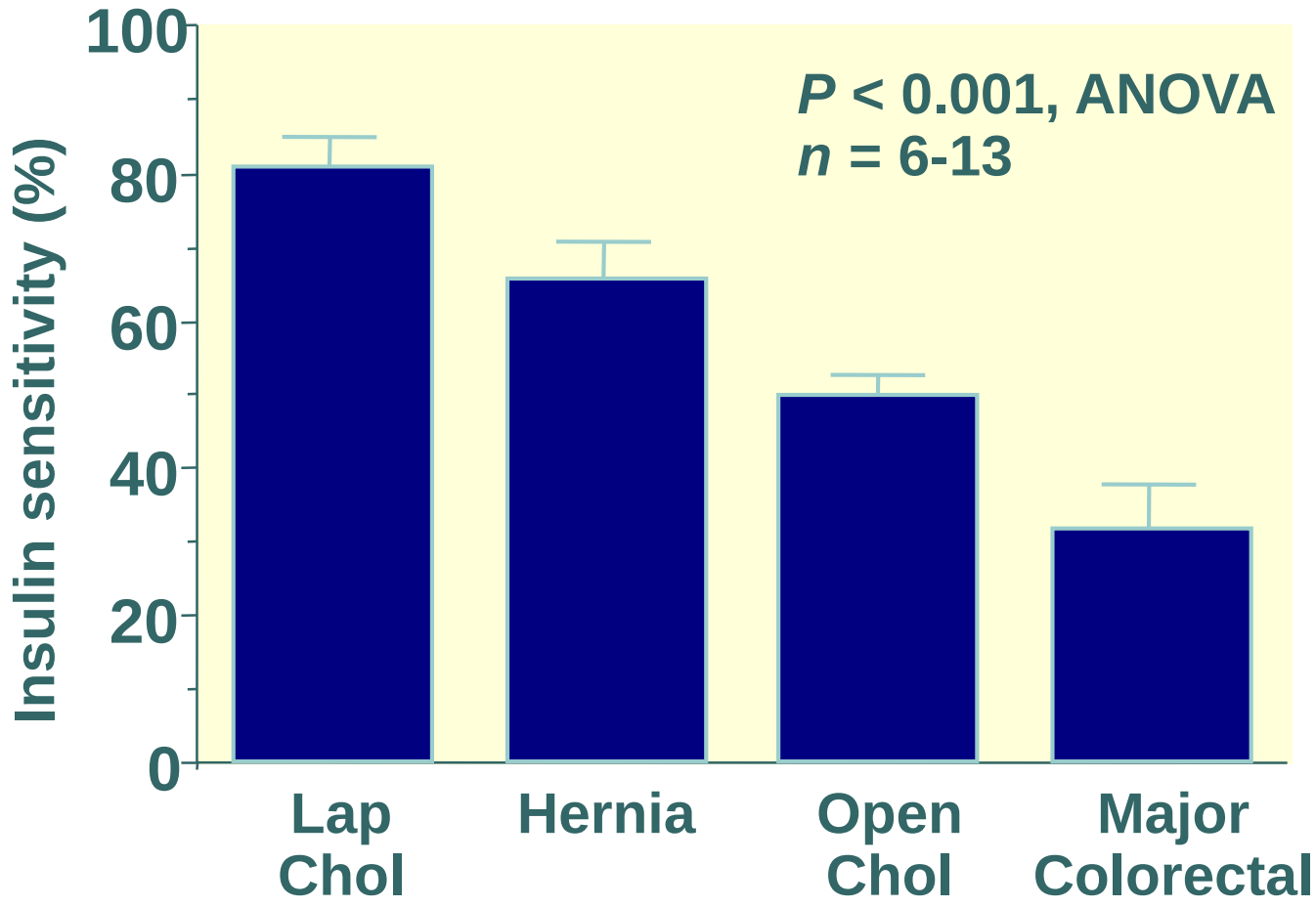
- Stress hormones
  - Catecholamines
  - Cortisol
  - Glucagon
  - (Growth hormone)
- Cytokines
  - TNF alpha
  - Interleukin-6

# Insulin resistance

- Reduced effect of insulin on glucose turnover –> Hyperglycemia

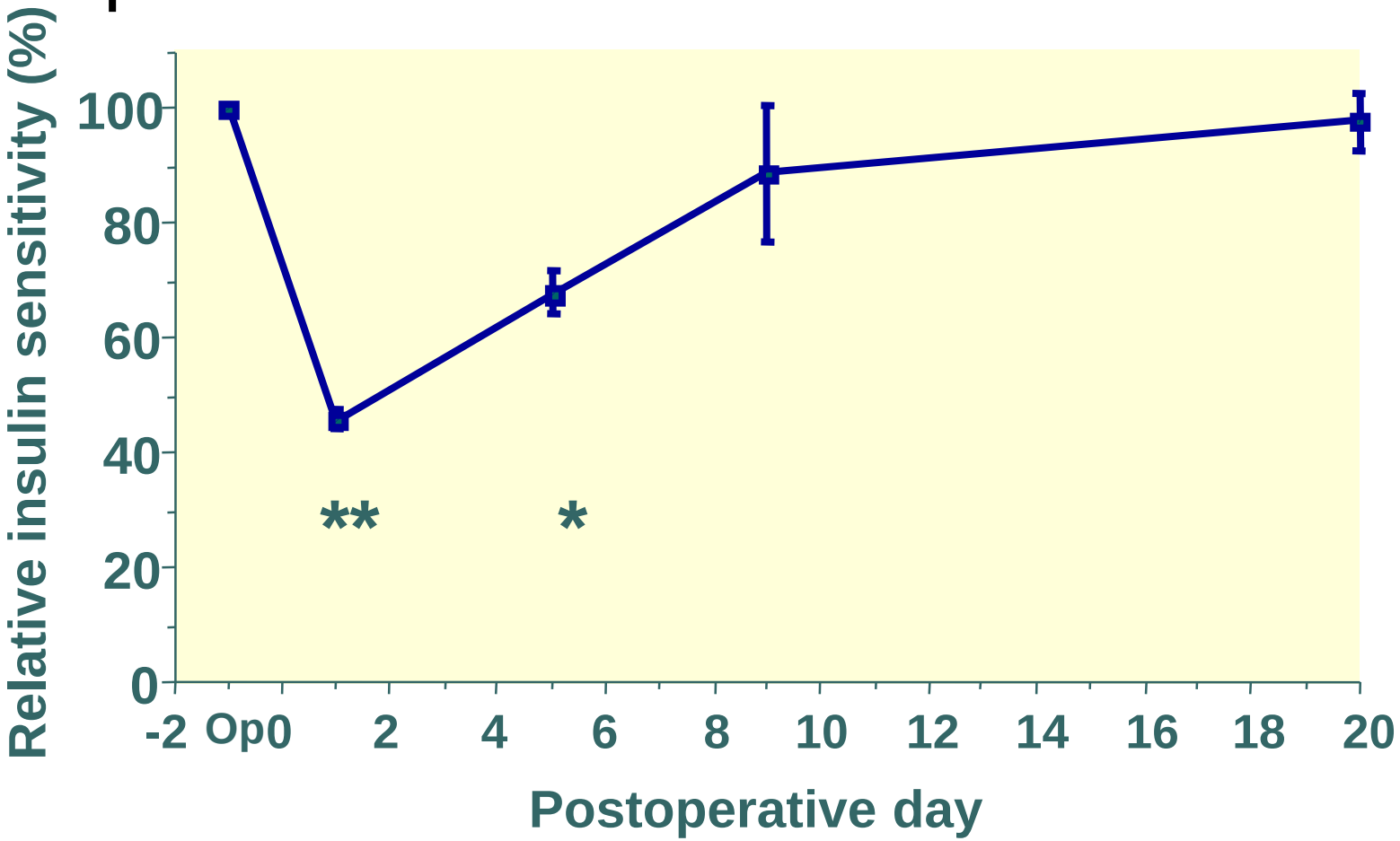
- Related to
  - Substrate oxidation
  - Lipolysis
  - Protein catabolism

# Insulin sensitivity and magnitude of operation



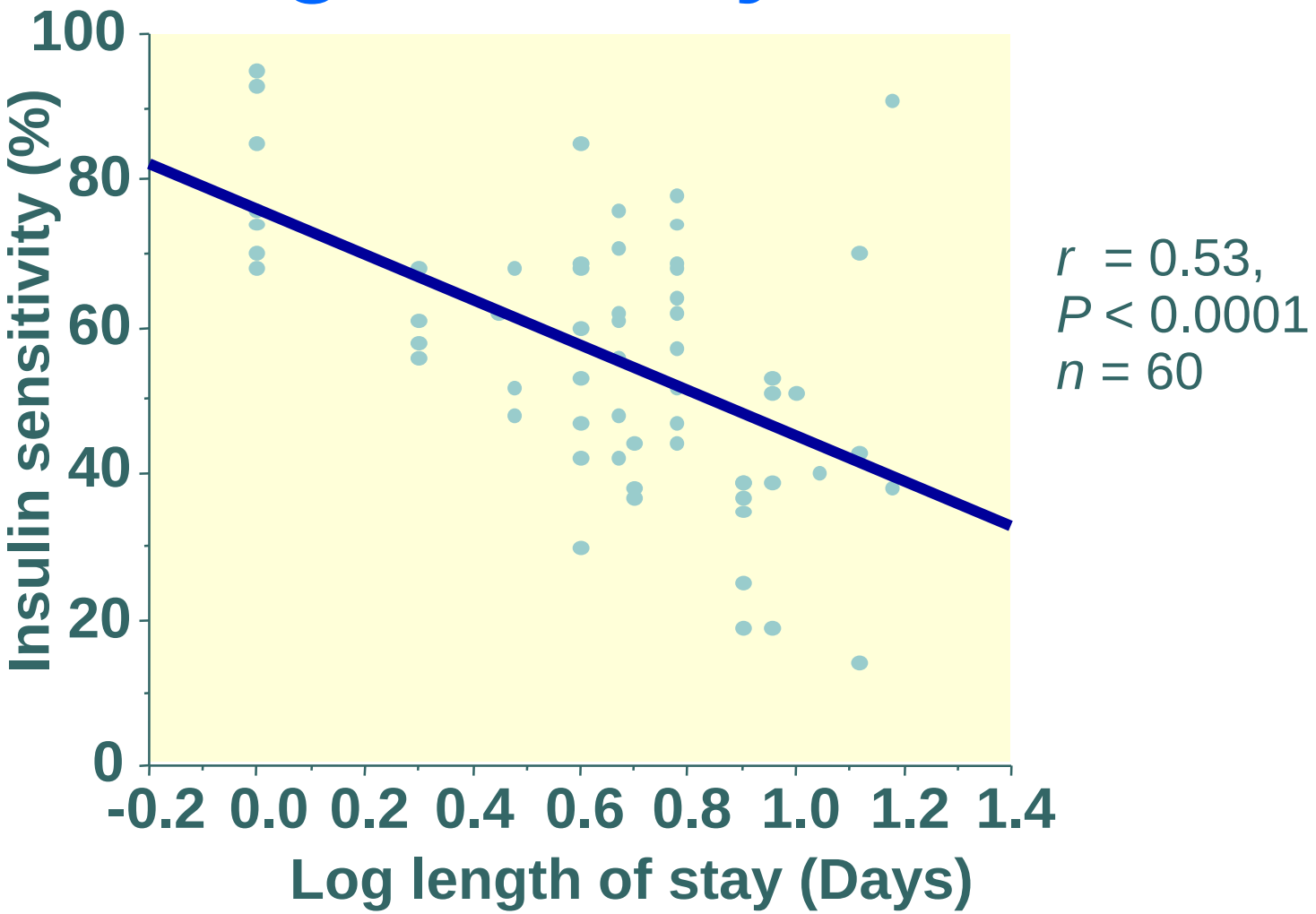

*Thorell et al: Curr Opin Clin Nutr Metab Care, 1999*

# Time course of insulin resistance




*Thorell et al: Curr Opin Clin Nutr Metab Care, 1999*

# Insulin resistance & length of stay




*Thorell et al: Curr Opin Clin Nutr Metab Care, 1999*

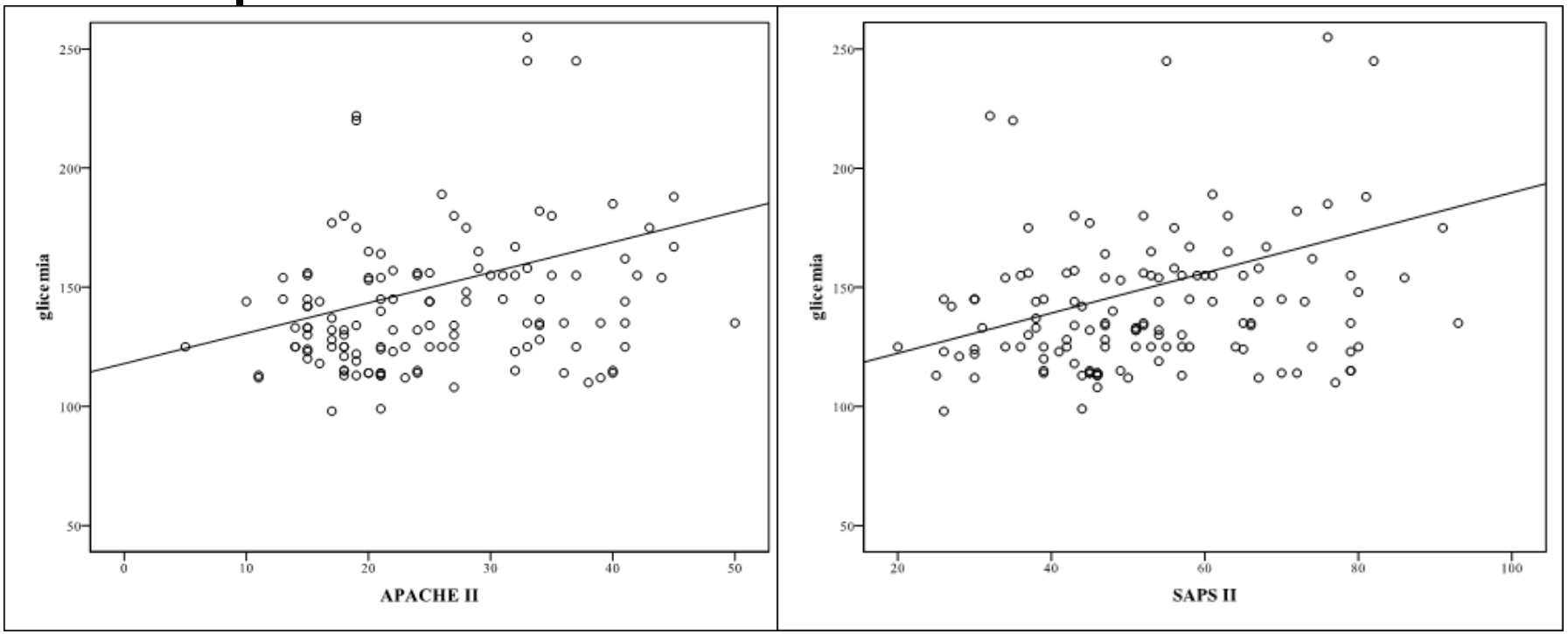
# Factors predicting length of stay

- Type of surgery
- Perioperative blood loss
- Postoperative insulin resistance

$R^2 = 0.71, p < 0.01$

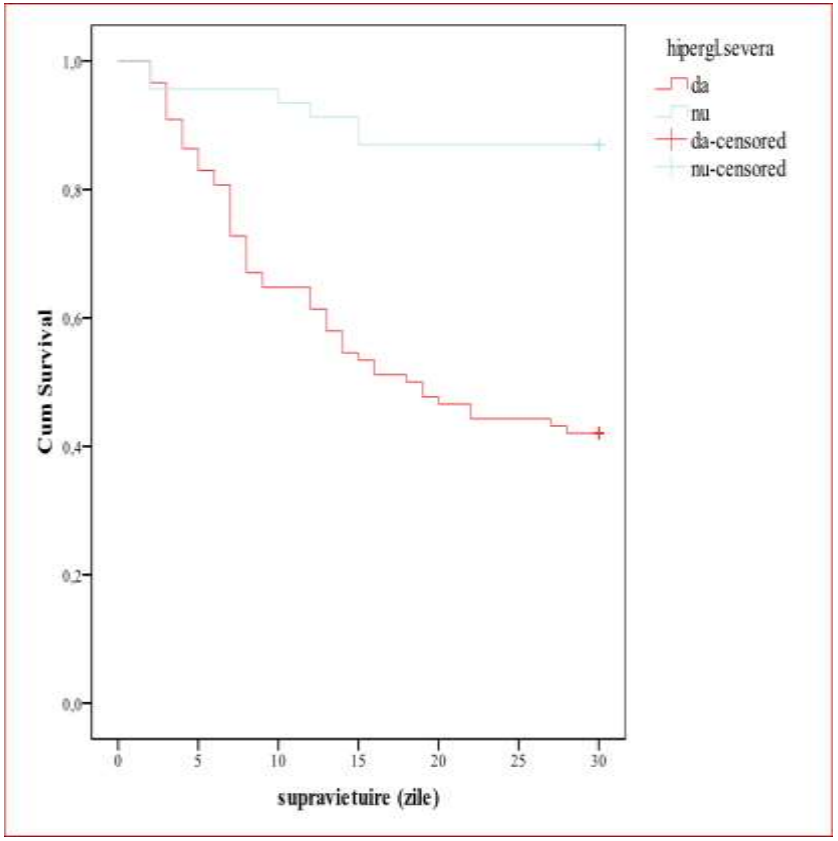
*Thorell et al: Curr Opin Clin Nutr Metab Care, 1999*

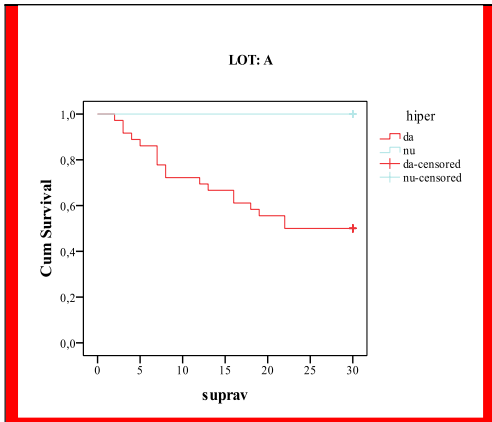
# Risk of hyperglycemia

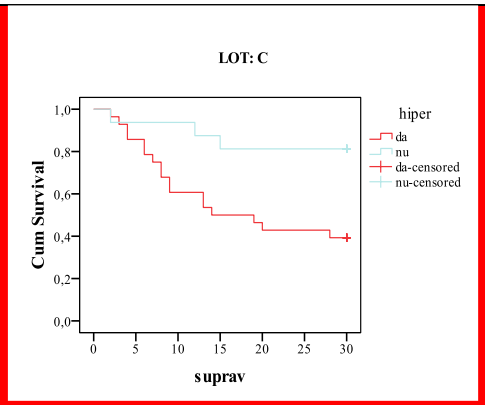



BG levels were strongly corelated with severity of septic shock estimated by APACHE II score (r=+0.241;p=0.005) or SAPS II (r=0.280;p=0.001) - Pearson Correlation

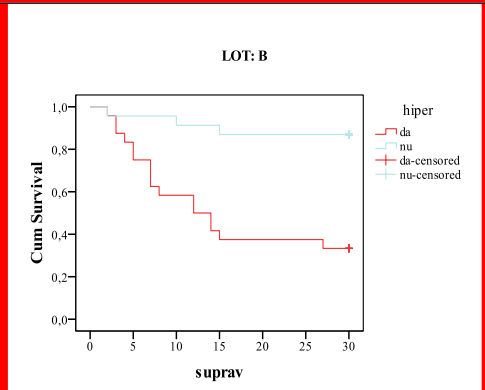
*Mirea L et al. Discontinuous corticosteroids administration increase the risk of hyperglycaemia in septic shock, Clinical Nutrition 2014; 33: S125*
*Mirea L et al. The impact of corticosteroids administration in septic shock on glycaemic variability, Crit Care 2014; A333*




| LOT | | p |
|---|---|---|
| A | Log Rank (Mantel-Cox) | ,029 |
| B | Log Rank (Mantel-Cox) | ,000 |
| C | Log Rank (Mantel-Cox) | ,011 |




*Mirea L et al. Discontinuous corticosteroids administration increase the risk of hyperglycaemia in septic shock, Clinical Nutrition 2014; 33: S125*
*Mirea L et al. The impact of corticosteroids administration in septic shock on glycaemic variability, Crit Care 2014; A333*

# Glycaemic variability

| | | | deces | | |
|---|---|---|---|---|---|
| | | | da | nu | Total |
| grupSD | p20 | Frecventa | 42 | 20 | 62 |
| | | % din grupSD | 67,7 % | 32,3 % | 100,0 % |
| | | % din deces | 73,7 % | 26,0 % | 46,3 % |
| | s20 | Frecventa | 15 | 57 | 72 |
| | | % din grupSD | 20,8 % | 79,2 % | 100,0 % |
| | | % din deces | 26,3 % | 74,0 % | 53,7 % |
| Total | | Frecventa | 57 | 77 | 134 |
| | | % din grupSD | 42,5 % | 57,5 % | 100,0 % |
| | | % din deces | 100,0 % | 100,0 % | 100,0 % |

*Mirea L et al. The impact of corticosteroids administration in septic shock on glycaemic variability, Crit Care 2014; A333*

# Insulin treatment in surgical ICU

Prospective randomized trial

1548 consecutive postop ICU patients

Target glucose 4.5-6.1 mM vs. treat >12mM

- Mortality ICU ↓ 43%
- Mortality in hospital ↓ 34%

*G van den Berghe, N Engl J Med 2001*

# Insulin treatment in surgical ICU

Prospective randomized trial

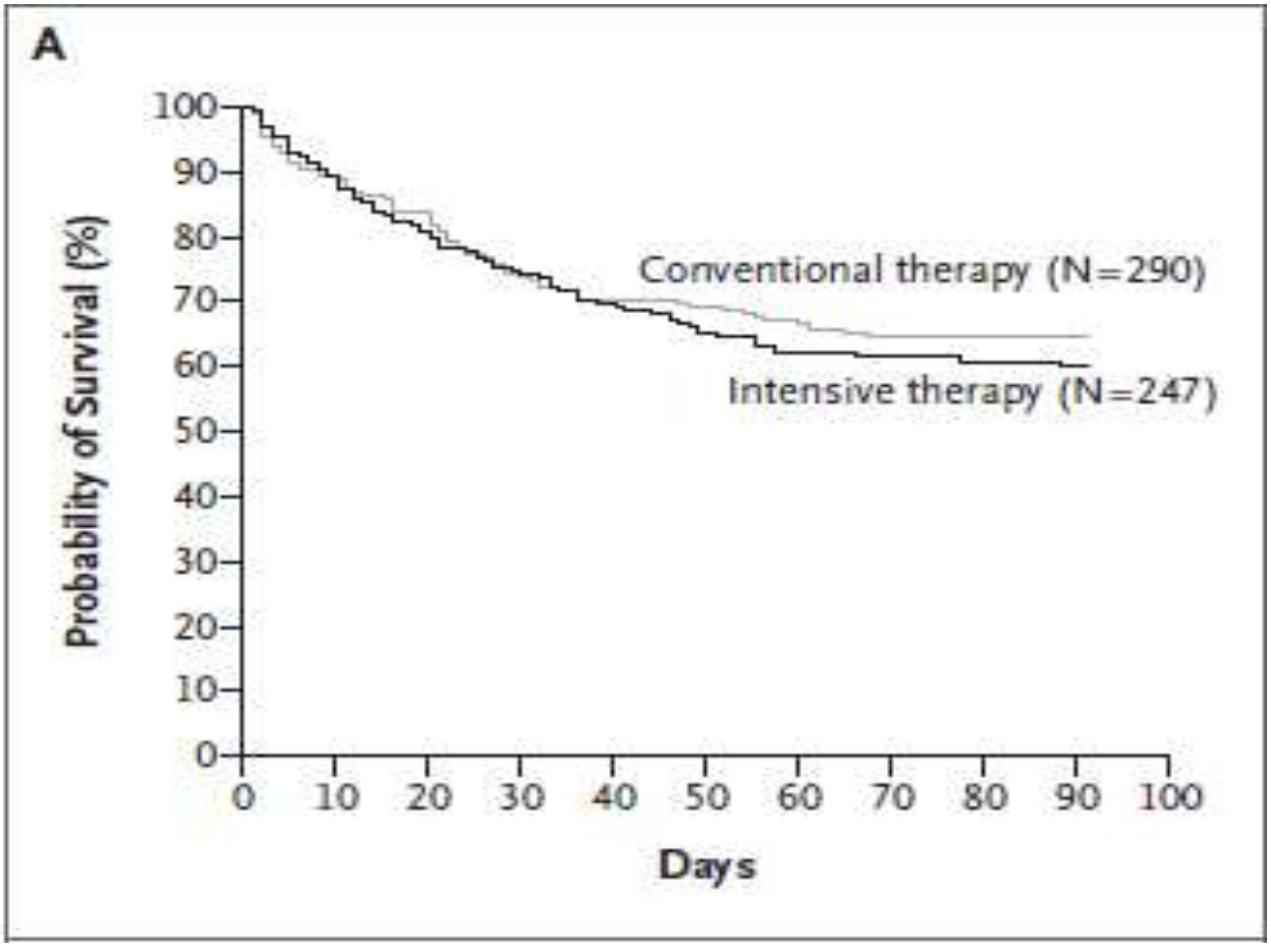
1548 consecutive postop ICU patients

Target glucose 4.5-6.1 mM vs. treat >12mM

- Bacteremia ↓ 46%
- Ventilatory support ↓ 37%
- Renal failure ↓ 41%
- Polyneuropathy ↓ 44%

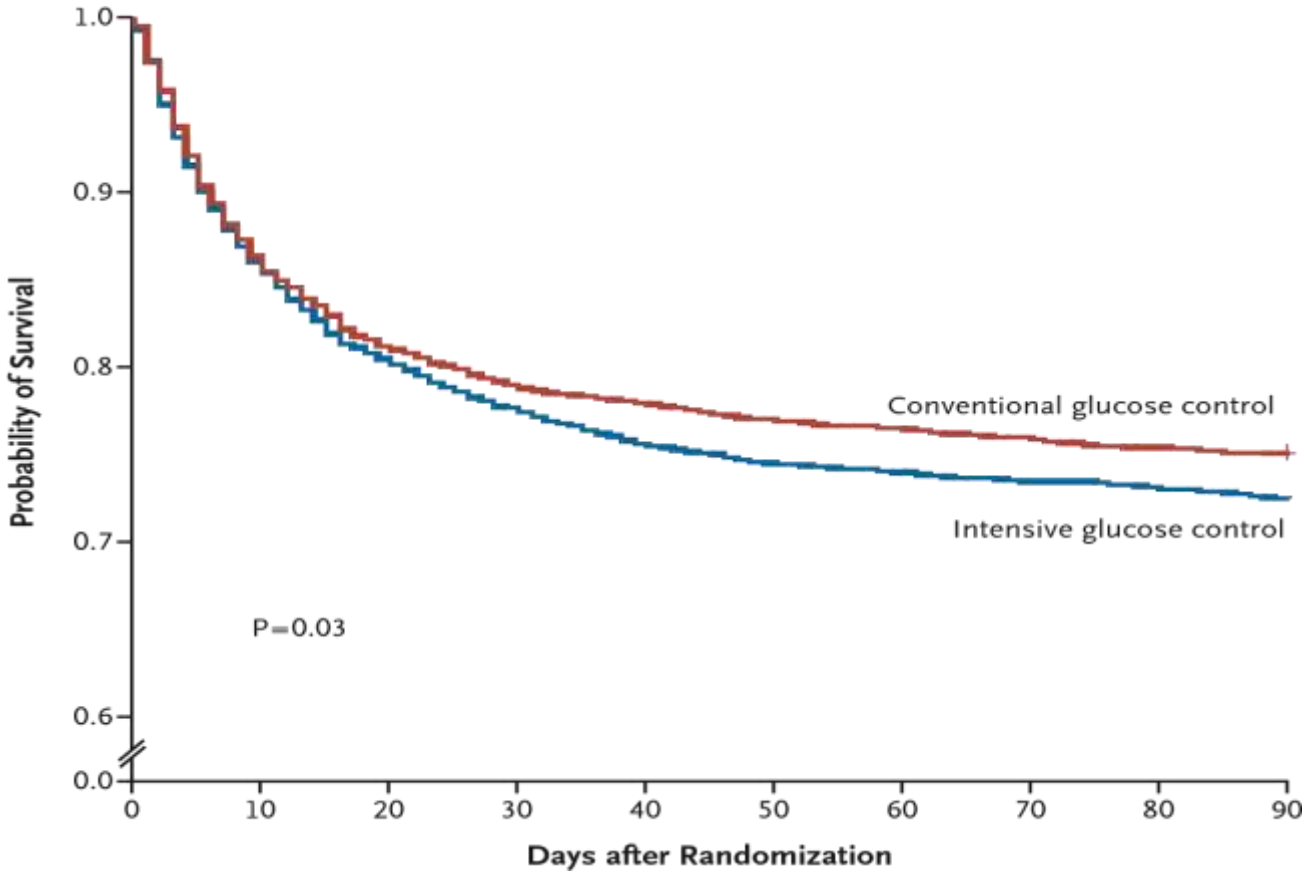
*G van den Berghe, N Engl J Med 2001*

# VISEP Trial, 2008



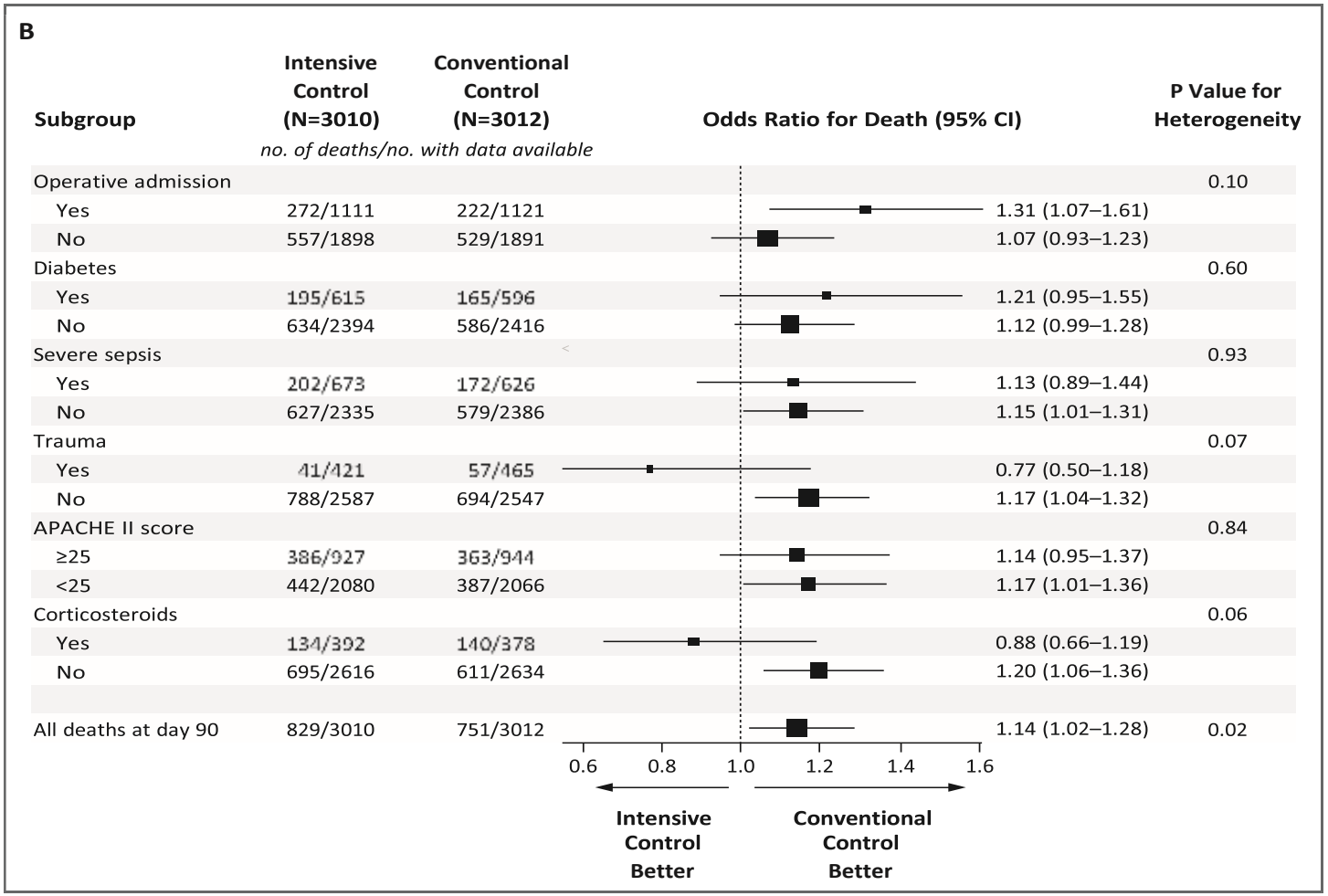

*Brunkhorst FM, Engel C, Bloos F, et al. N Engl J Med 2008, 358:125-139*

# NICE SUGAR 1



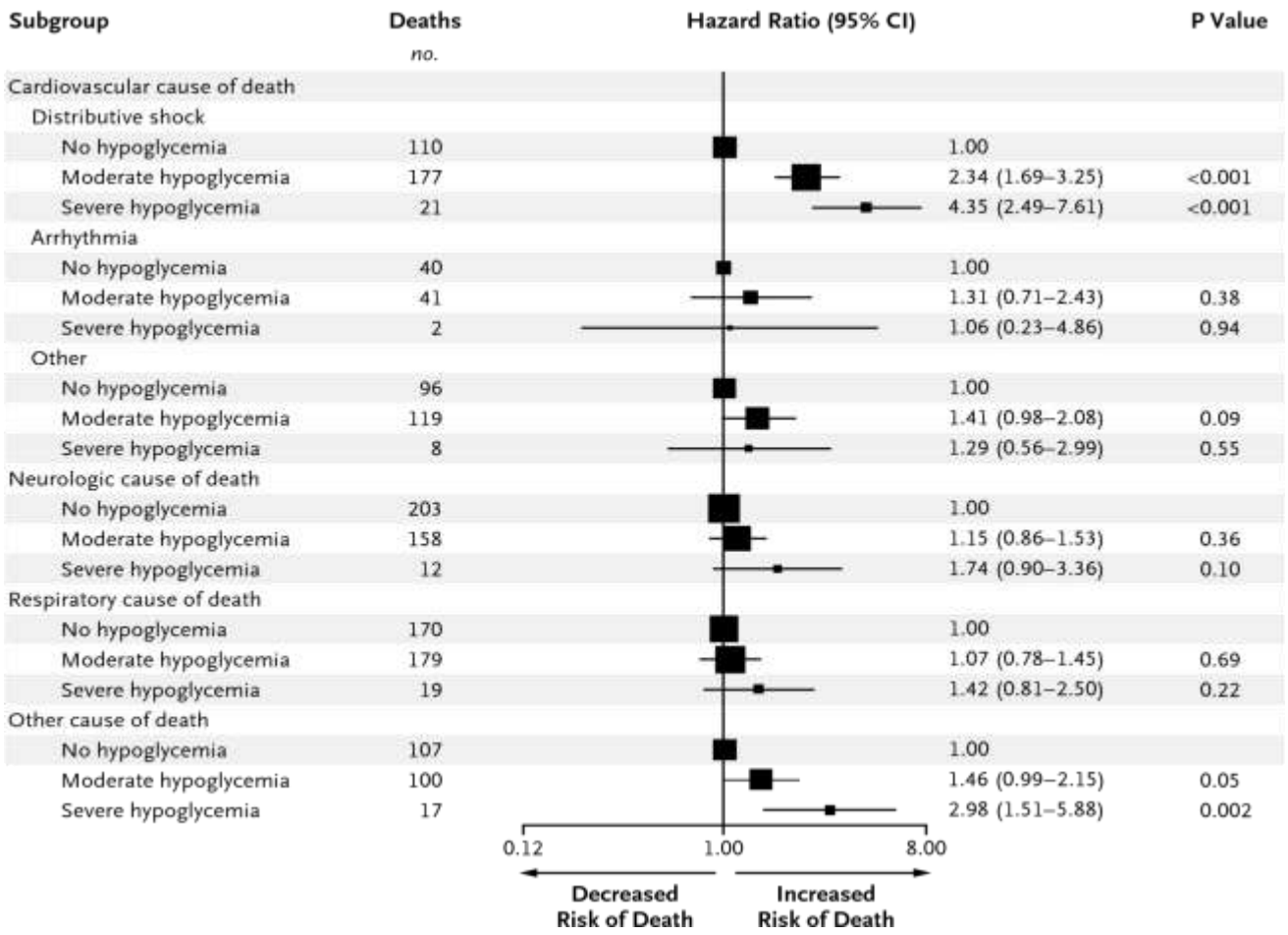

*Finfer S et al. N Engl J Med 2009;360:1283-97*

# NICE SUGAR 1




*Finfer S et al. N Engl J Med 2009;360:1283-97*

# NICE SUGAR 2




*Finfer S et al. N Engl J Med 2012;367:1108-18*

# Metanalysis

- Griesdale et al., 2009
- Friedrich et al., 2010
- Wiener et al., 2008
- Marik et al., 2010
- Kansagara et al., 2011

Griesdale DE, de Souza RJ, van Dam RM, et al. CMAJ 2009; 180:821–827
Friedrich JO, Chant C, Adhikari NK. Crit Care 2010; 14:324
Wiener RS, Wiener DC, Larson RJ. JAMA 2008; 300:933–944
Marik PE, Preiser JC. Chest 2010; 137:544–551
Kansagara D, Fu R, Freeman M, et al. 154:268–282

# Normoglycemia

- Preiser JC “Restoring normoglycemia: not so harmless”

(Crit Care 2008, 12:116)

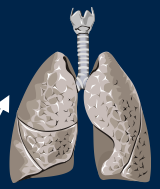
# Actual recommendations

- Start insulin drip protocol when 2 consecutive BG > 180mg/dL
- Glucose goal ≤ 180 mg/dL, not ≤ 110 mg/dL BG
- monitoring every 1-2 hour until stable, then q4hrs after
- Capillary BG may not be as accurate as blood BG

*Dellinger RP, Gerlach H, Douglas I et al. Surviving Sepsis Campaign Critical Care Medicine 2013; 41(2): 580- 640, www.ccmjournal.org*

# Glutamine supplementation

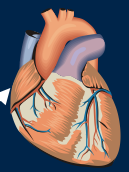
# Effects of Glutamine



major energy source for endothelial cell -Jing 2007

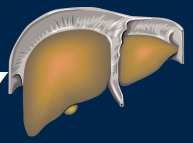
↓ALI / ARDS in sepsis - Singleton 2005

protection to oxidative stress - Kelly 2003



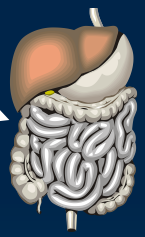
major energy source for miocyte - Kelly 2003

protection to ischemia-reperfusion injury - Khogali 2002



glutathione synthesis

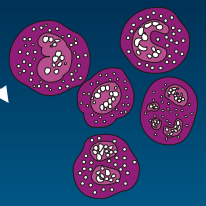
regulatory for nitrogen metabolism - Kelly 2003



major energy source for mucosal cell, ↑ IgA -Singleton 2007

maintains structure (van der Hulst 1993), integrity and permeability of intestinal mucoasa - de Souza 2005

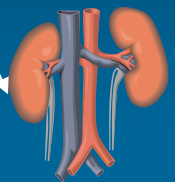
protection to oxidative stress, antiapoptotic -Singleton 2007



major energy source

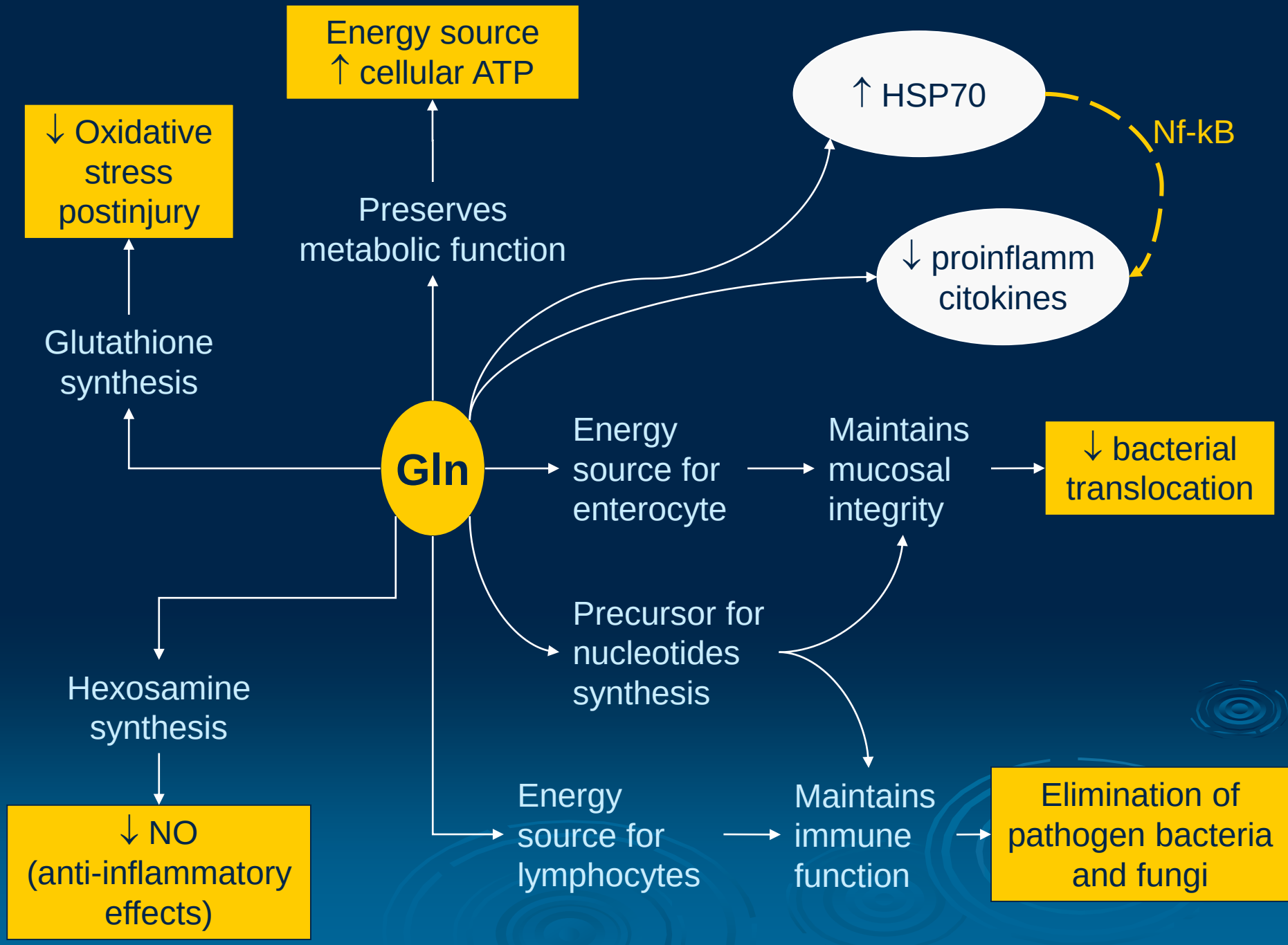
stimulates PMN and macrophages - Singleton 2007

↓ Synthesis of proinflammatory citokines and peroxide



acid-base regulation

$NH_3$ metabolism



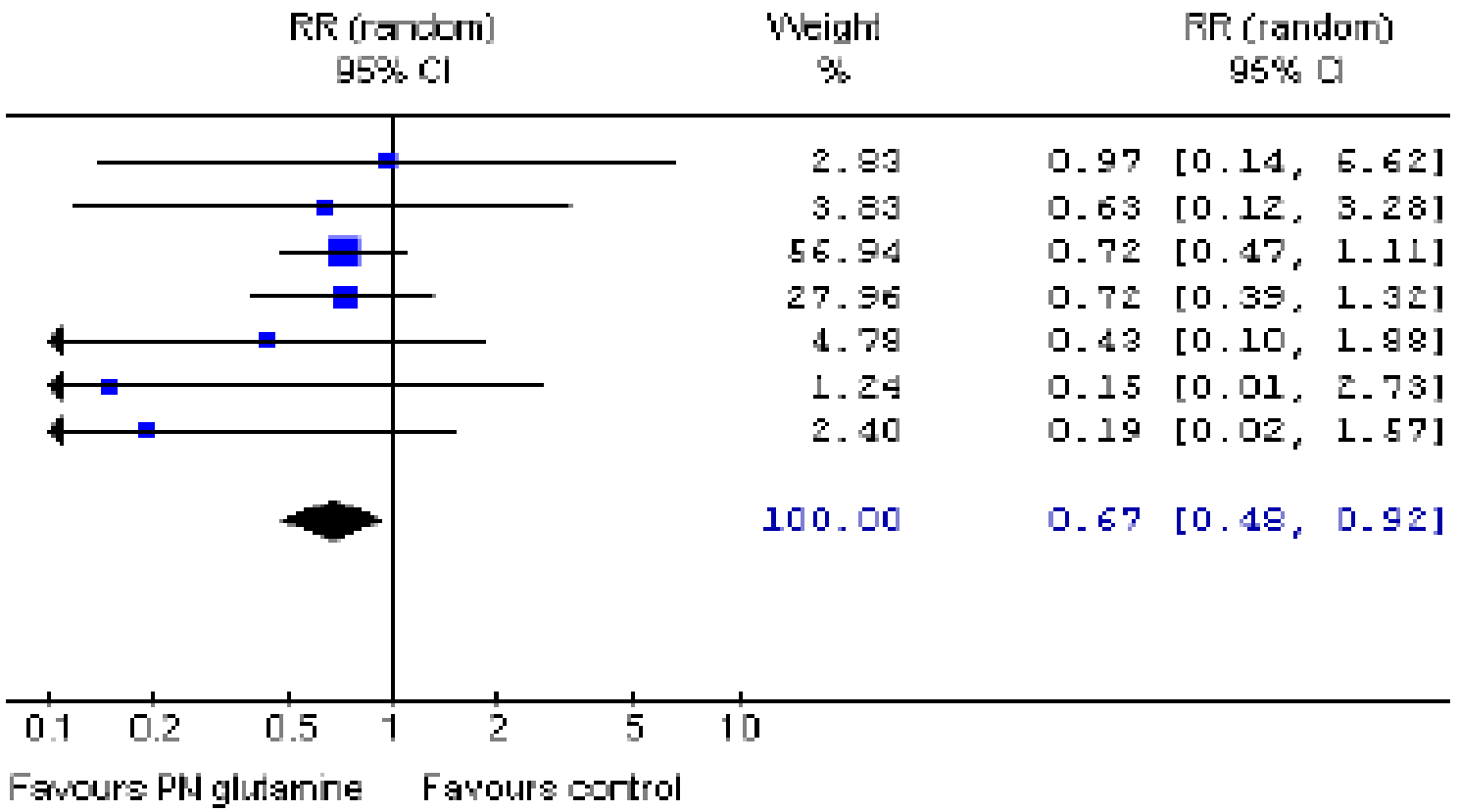

modified after Kelly & Wischmeyer 2003

# Parenteral Glutamine vs Control

## Mortality

**Study**

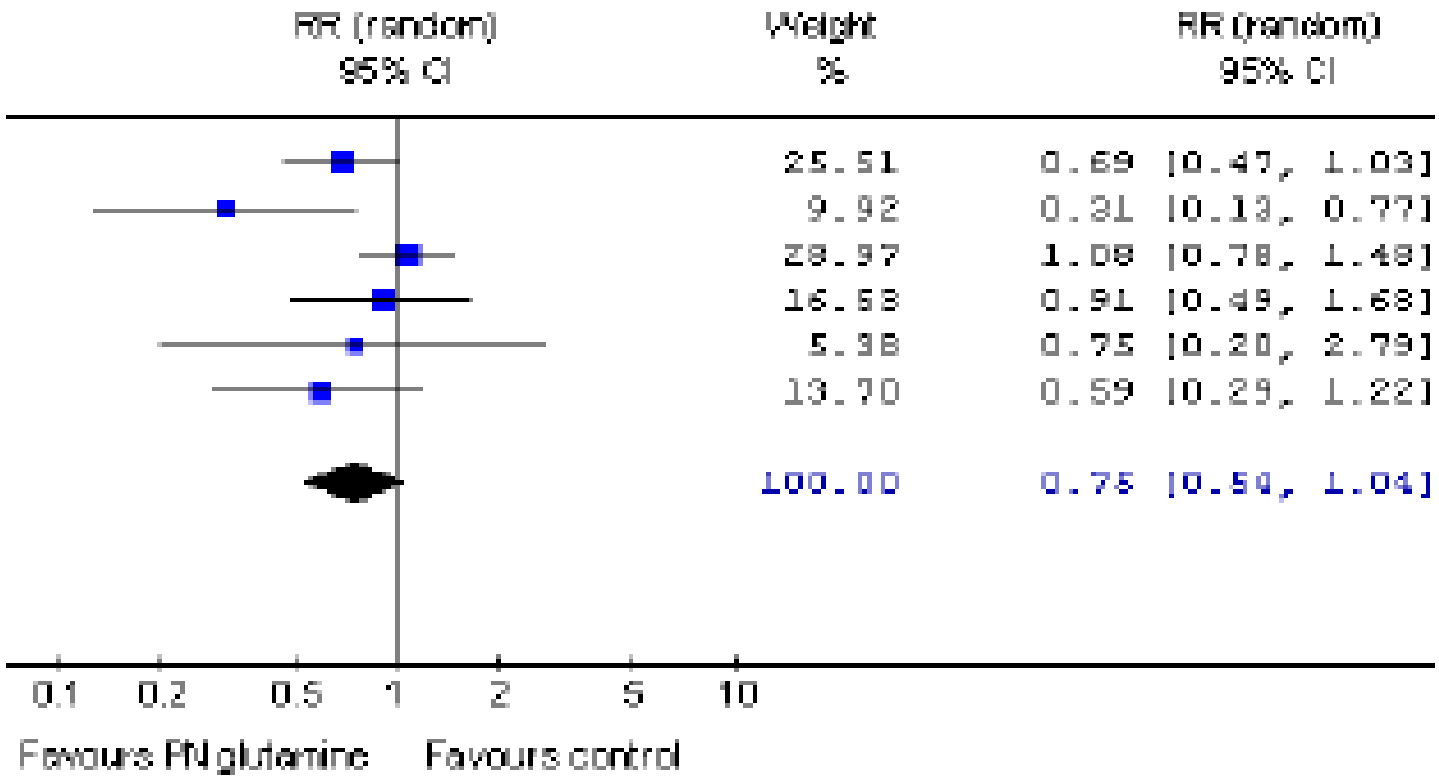
- Dechelotte 2006
- Fuentes-Orozco 2004
- Griffiths 1997
- Powell-Tuck 1999
- Wischmeyer 2001
- Xian-Li 2004
- Ziegler unpub



# Parenteral Glutamine vs Control
## Infectious Complications

**Study**

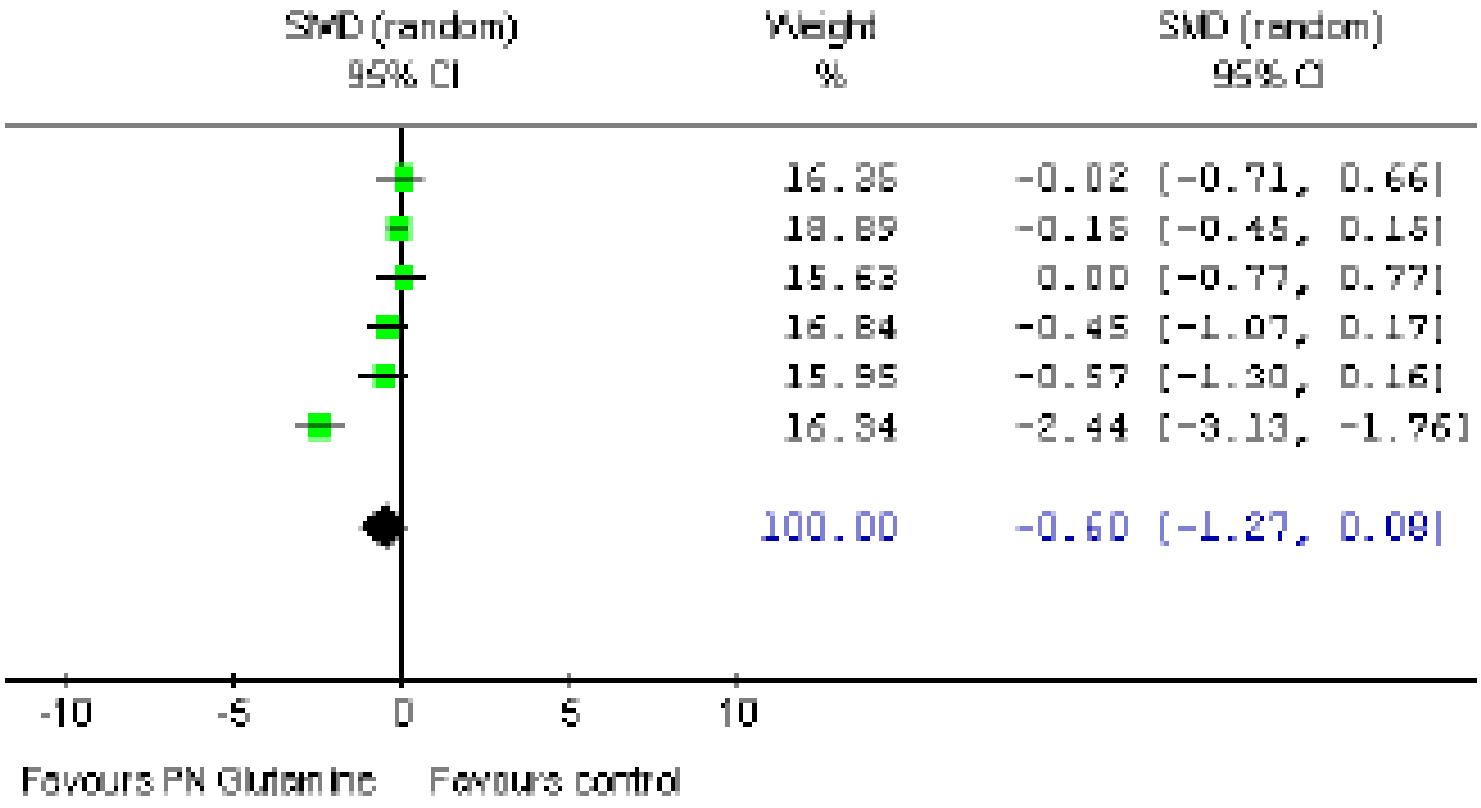
- Dechelotte 2006
- Fuentes-Orozco 2004
- Griffiths 1997
- Wischmeyer 2001
- Zhou 2004
- Ziegler unpub



# Parenteral Glutamine vs Control
## Length of Hospital Stay

**Study**

- Fuentes-Orozco 2004
- Powell-Tuck 1999
- Wischmeyer 2001
- Xian-Li 2004
- Zhou 2004
- Ziegler unpub



# Safety and Tolerance

- No study ever demonstrated any adverse effects at Gln supplementation in healthy volunteers or in patients (critically ill, surgical, etc)!

  Avenell A. Proc Nutr Soc 2006;65:236-241.

- Even supra-physiological levels are well tolerated

  Albers S et al. Clin Sci 1988;75:463-468.

- Ideally: monitoring daily plasma levels (concentration > 0.42 mmol/l) $\rightarrow$ only for detecting lower levels

  Wernerman J. Clin Nutr Suppl 2004;1:37-42.

- Patients with severe head trauma (GCS<8 and cerebral edema) - Gln supplementation doesn't modify intracerebral glutamate !!!

  Berg A et al. Intens Care Med 2006;32:1741-1746.

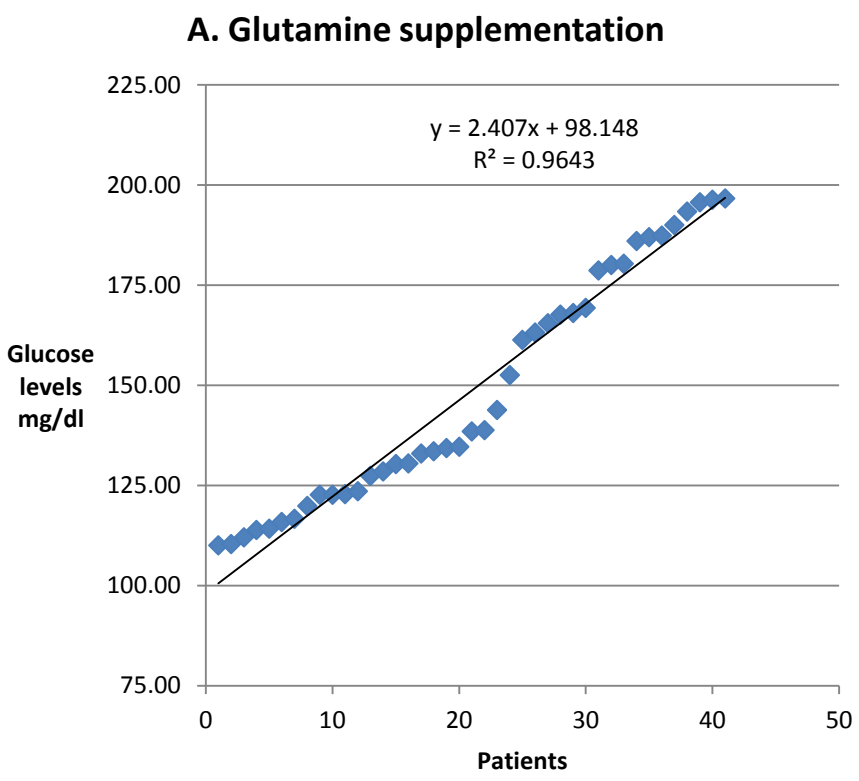
# Guidelines & Recommendations

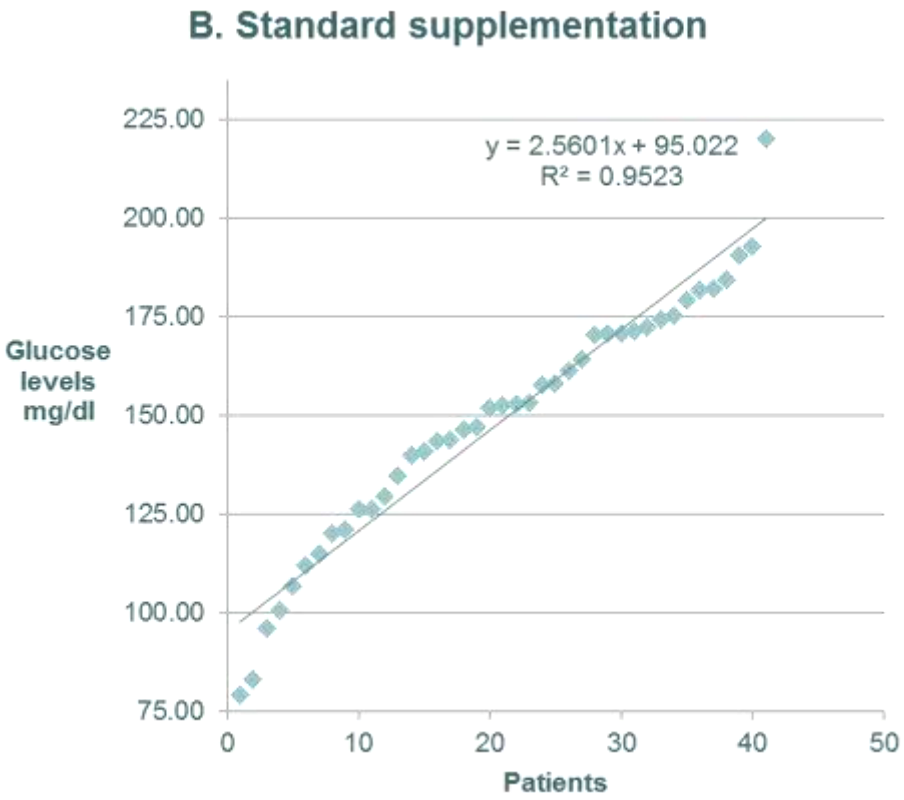
- All patients on parenteral nutrition should receive supplemental parenteral glutamine.
- In patients on enteral nutrition, parenteral glutamine might be supplemented.
- There is not enough evidence up to now to recommend enteral glutamine supplementation in all critically ill patients.
- Enteral glutamine is recommended in trauma and burn patients.

***0.2 - 0.57 g/kg/day, starting within first 24 hs, for at least 7 days***

*Goeters C et al. Crit Care Med 2002;30:9*

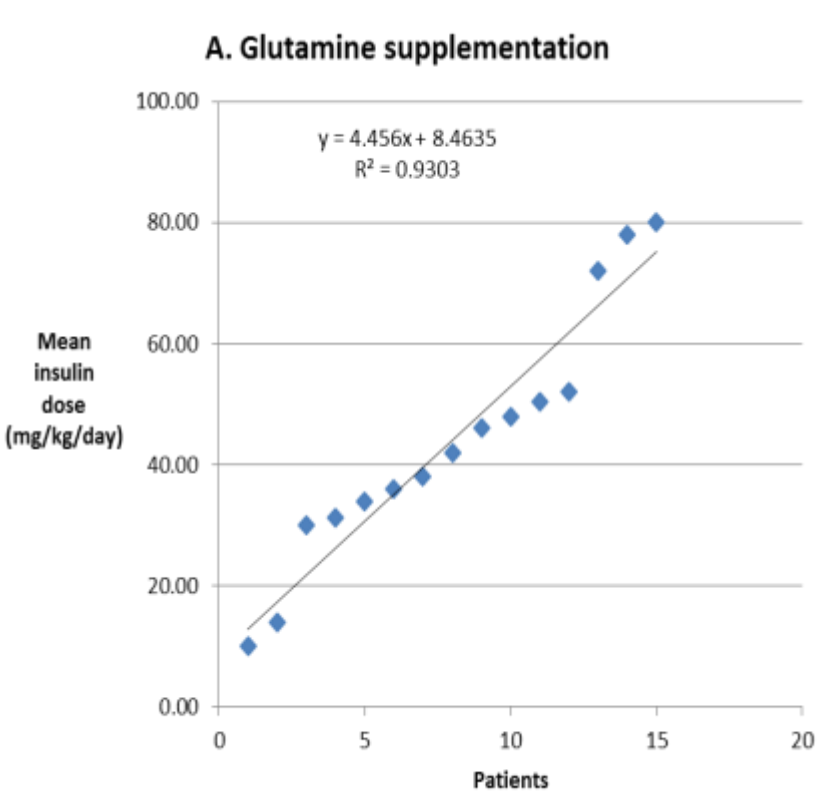
# Glutamine supplementation

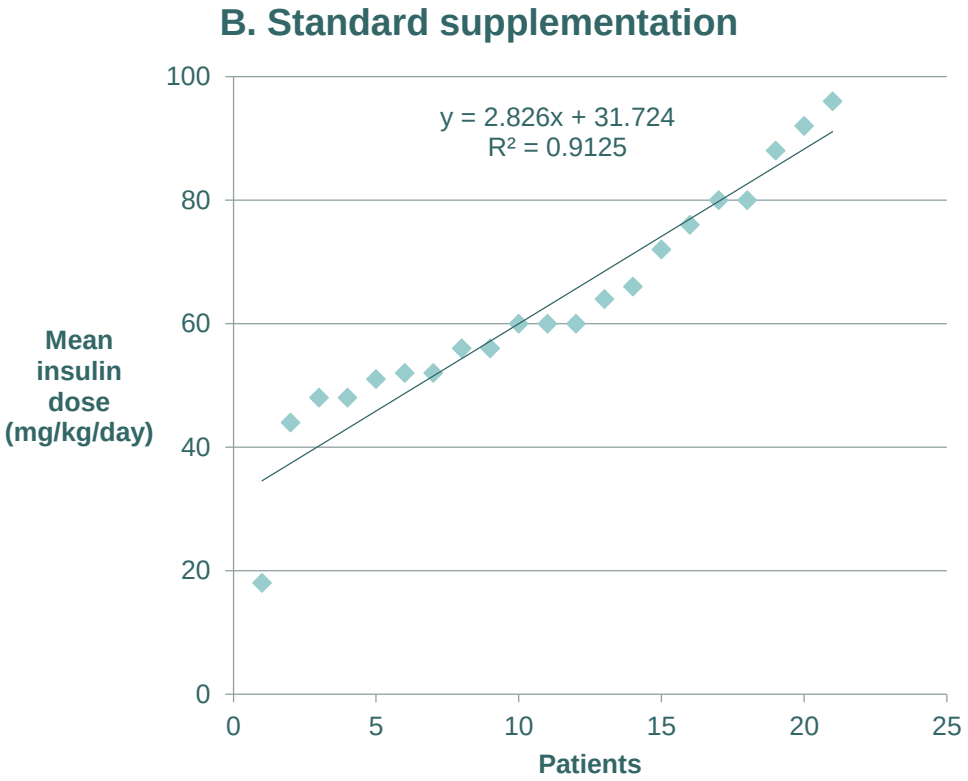



*Grintescu I et al. The influence of parenteral glutamine supplementation on glucose homeostasis in critically ill polytrauma patients—A randomized-controlled clinical study, Clinical Nutrition 2014 (articol in press)*

# Glutamine supplementation




*Grintescu I et al. The influence of parenteral glutamine supplementation on glucose homeostasis in critically ill polytrauma patients—A randomized-controlled clinical study, Clinical Nutrition 2014 (articol in press)*

# Conclusions- EN

- If EN is started early, a higher proportion of ICU patients can be adequately nourished enterally after a few days
- The literature suggests that EN should be started within the first 24 hours
- Only a few CI for EN
- Not so severe complications

# Conclusions- TPN

- Severe complications
- Not reduce mortality and overall morbidity
- Expensive


Thank you!

# 14- 16 noiembrie 2014
# Al 15-lea Simpozion Național de Nutriție Clinică

# 1-7 November 2015 – București
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