Should I start EN if a patient has gut dysfunction:

Dr Gordon S. Doig,
Associate Professor in Intensive Care,
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University of Sydney, Sydney, Australia
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Can early EN *prevent* gut dysfunction?

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Effect of Evidence-Based Feeding Guidelines on Mortality of Critically Ill Adults

A Cluster Randomized Controlled Trial

CARING FOR THE CRITICALLY ILL PATIENT

JAMA, December 17, 2008—Vol 300, No. 23

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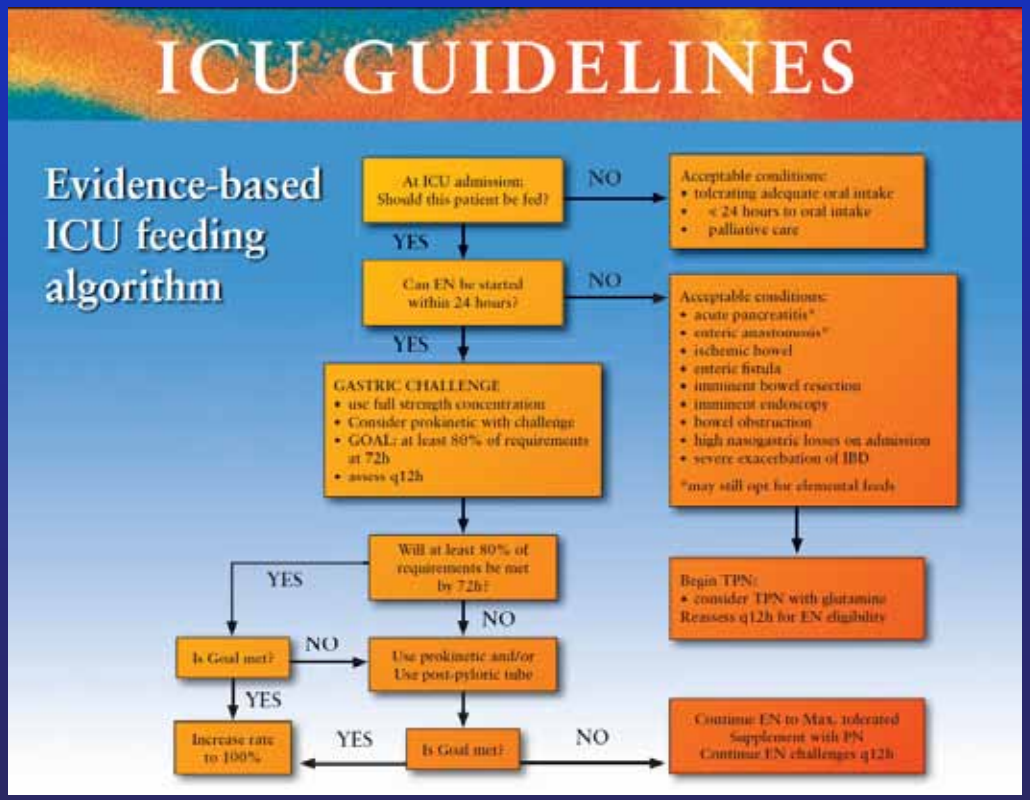
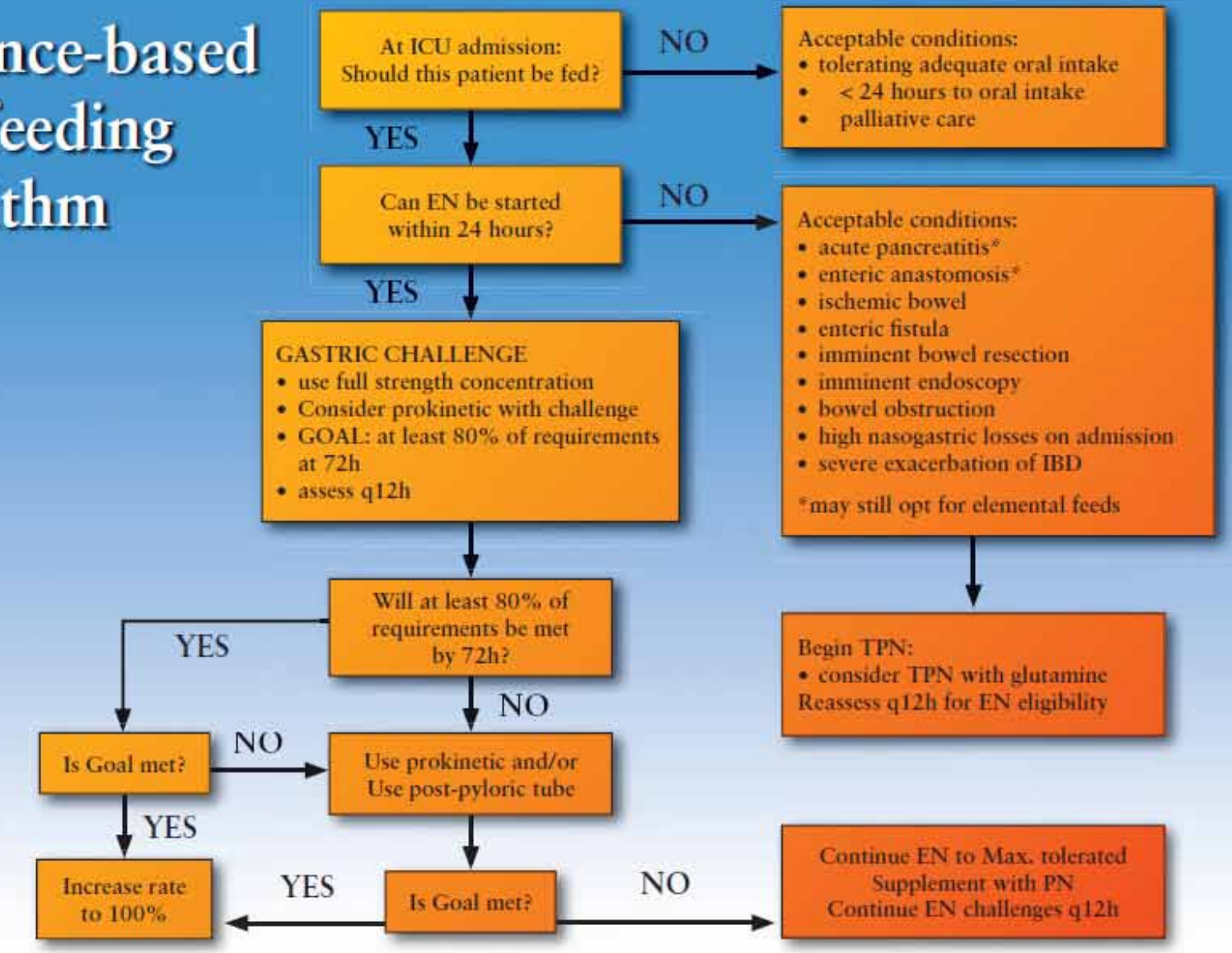


ICU GUIDELINES

Evidence-based ICU feeding algorithm



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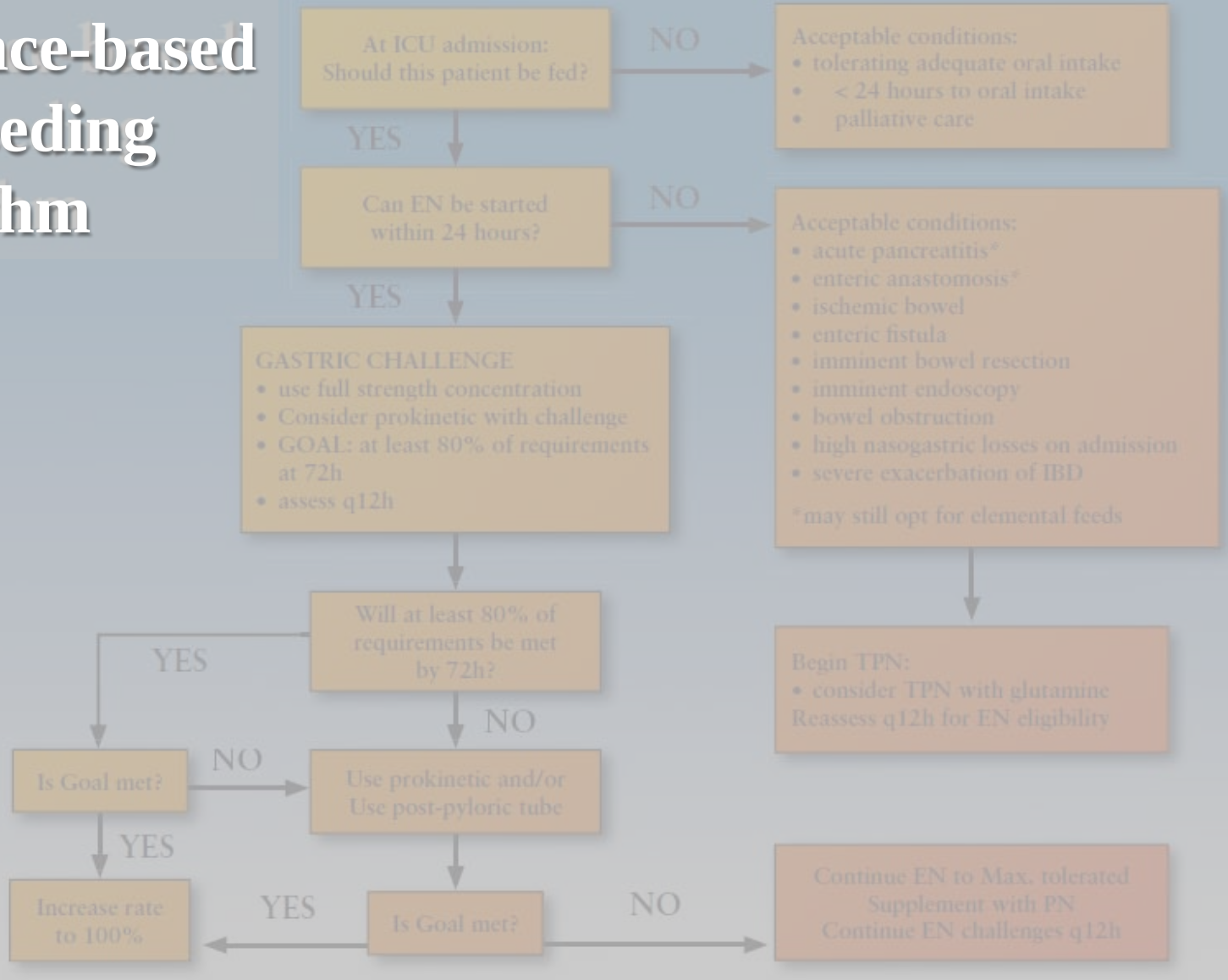

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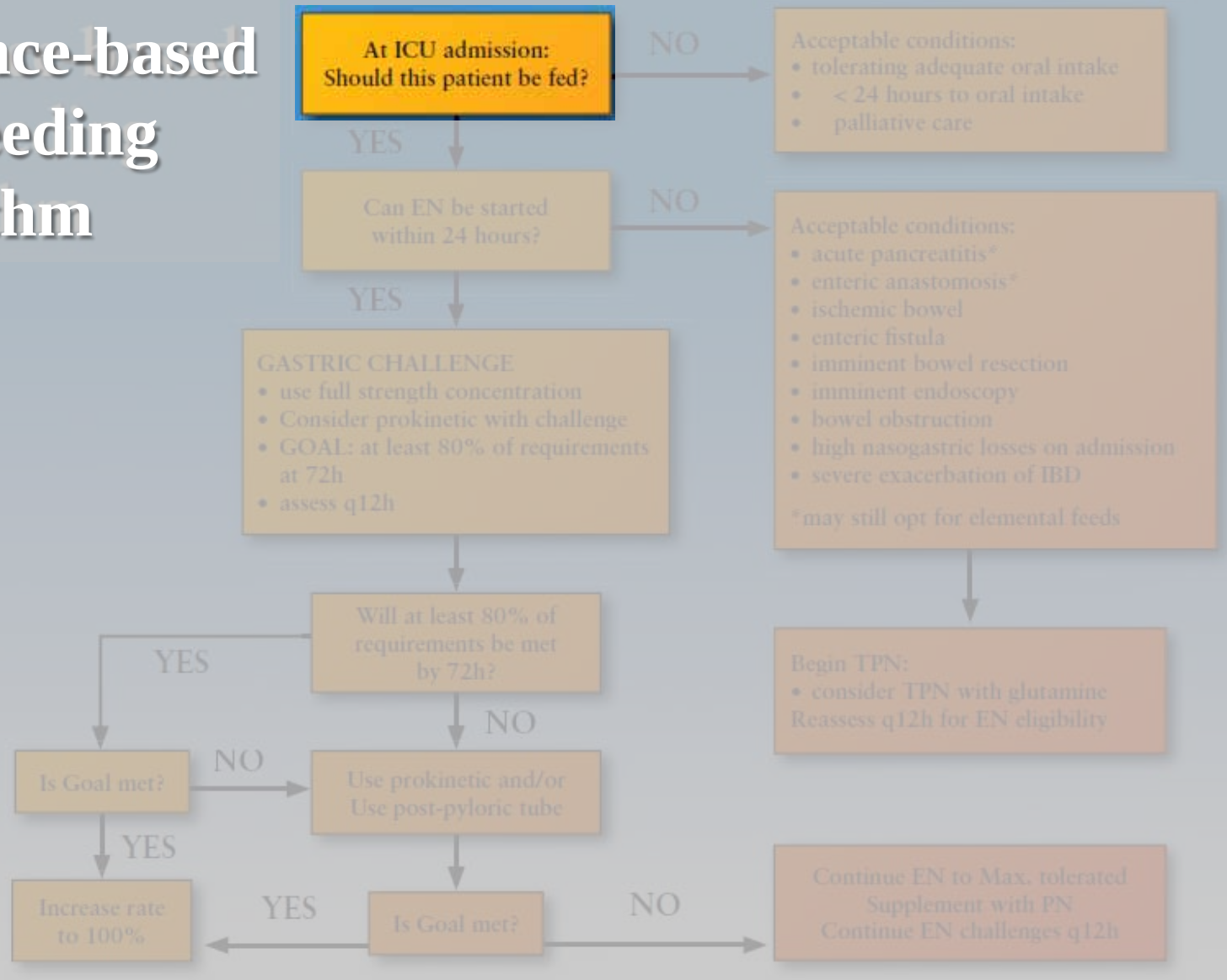

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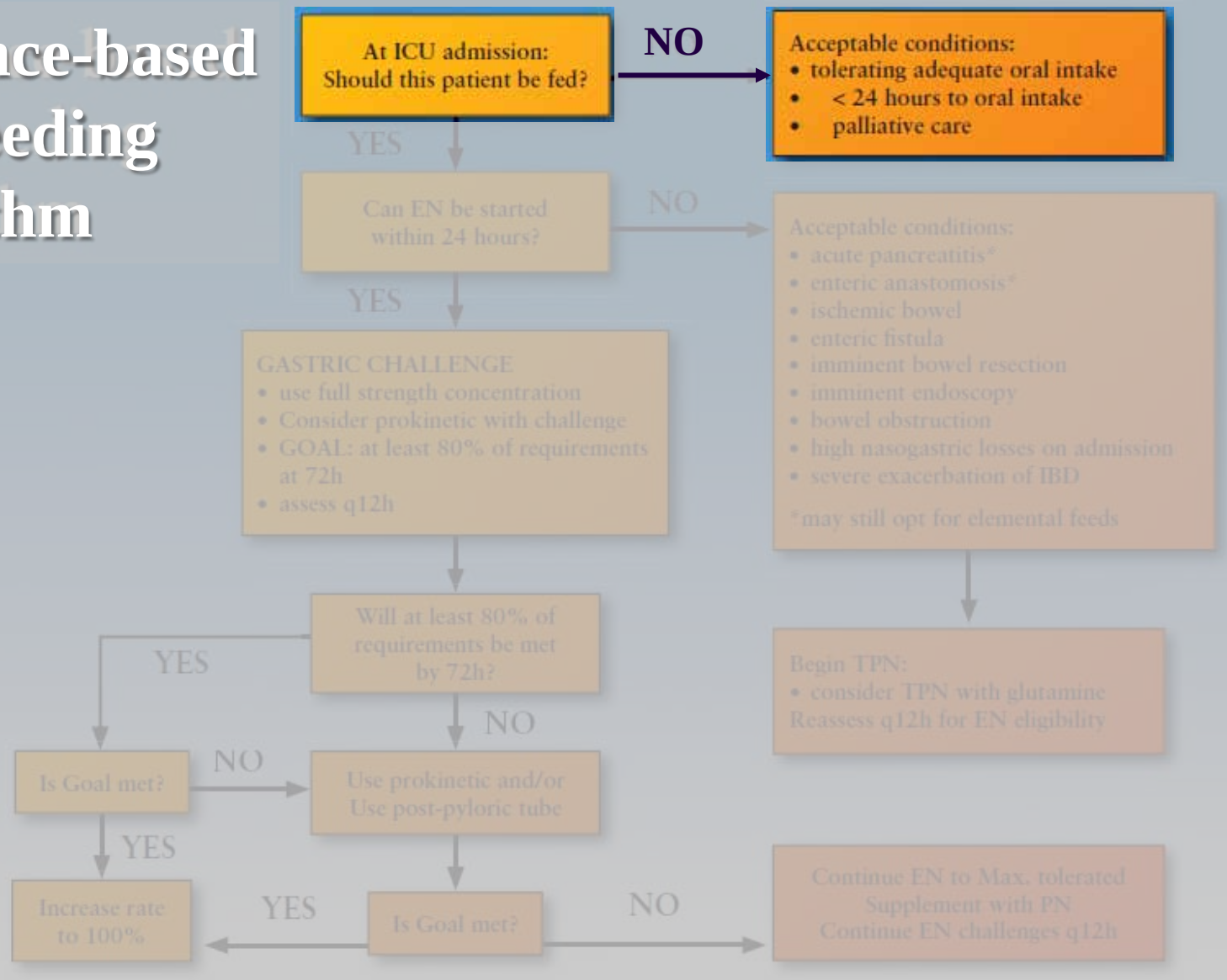

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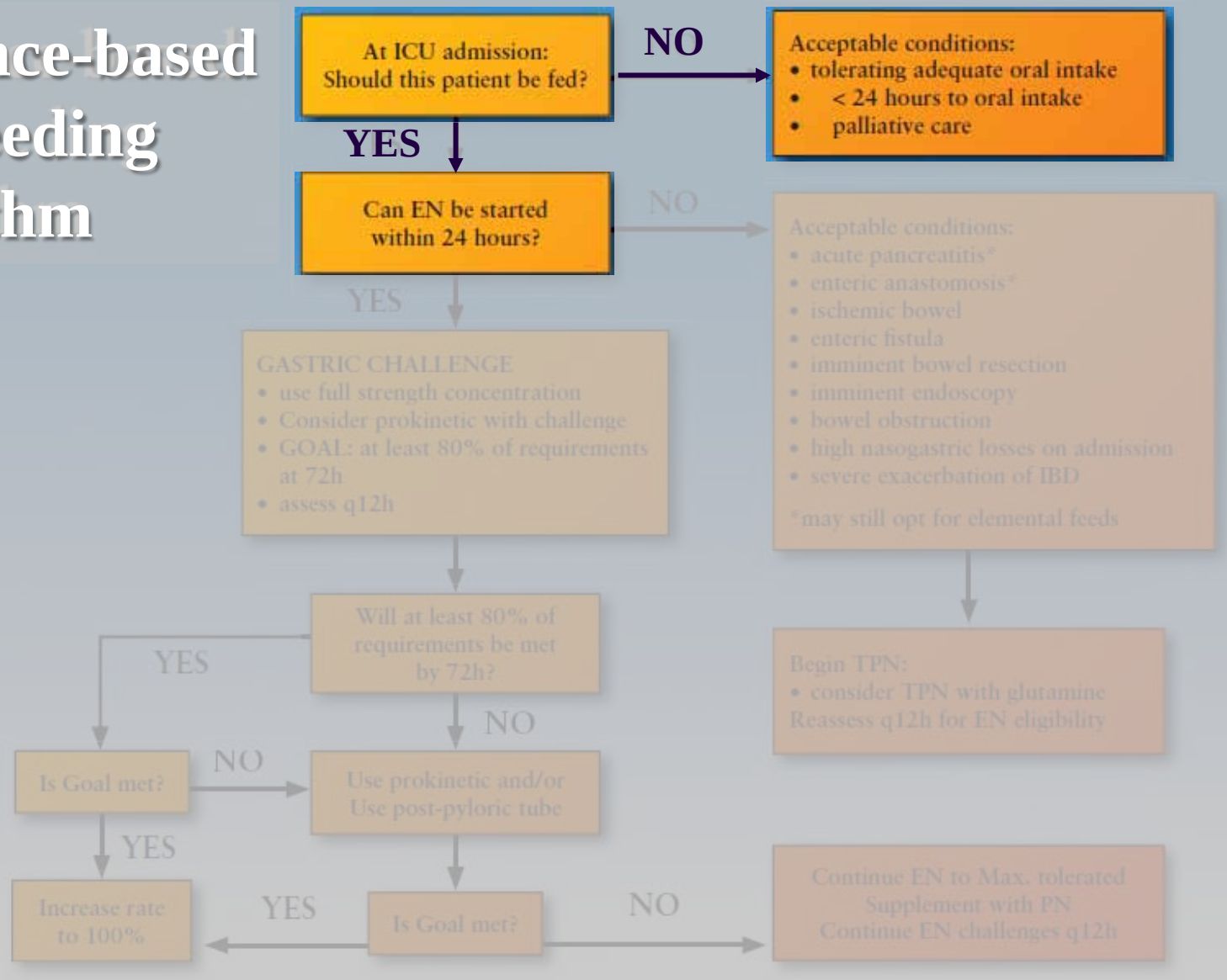

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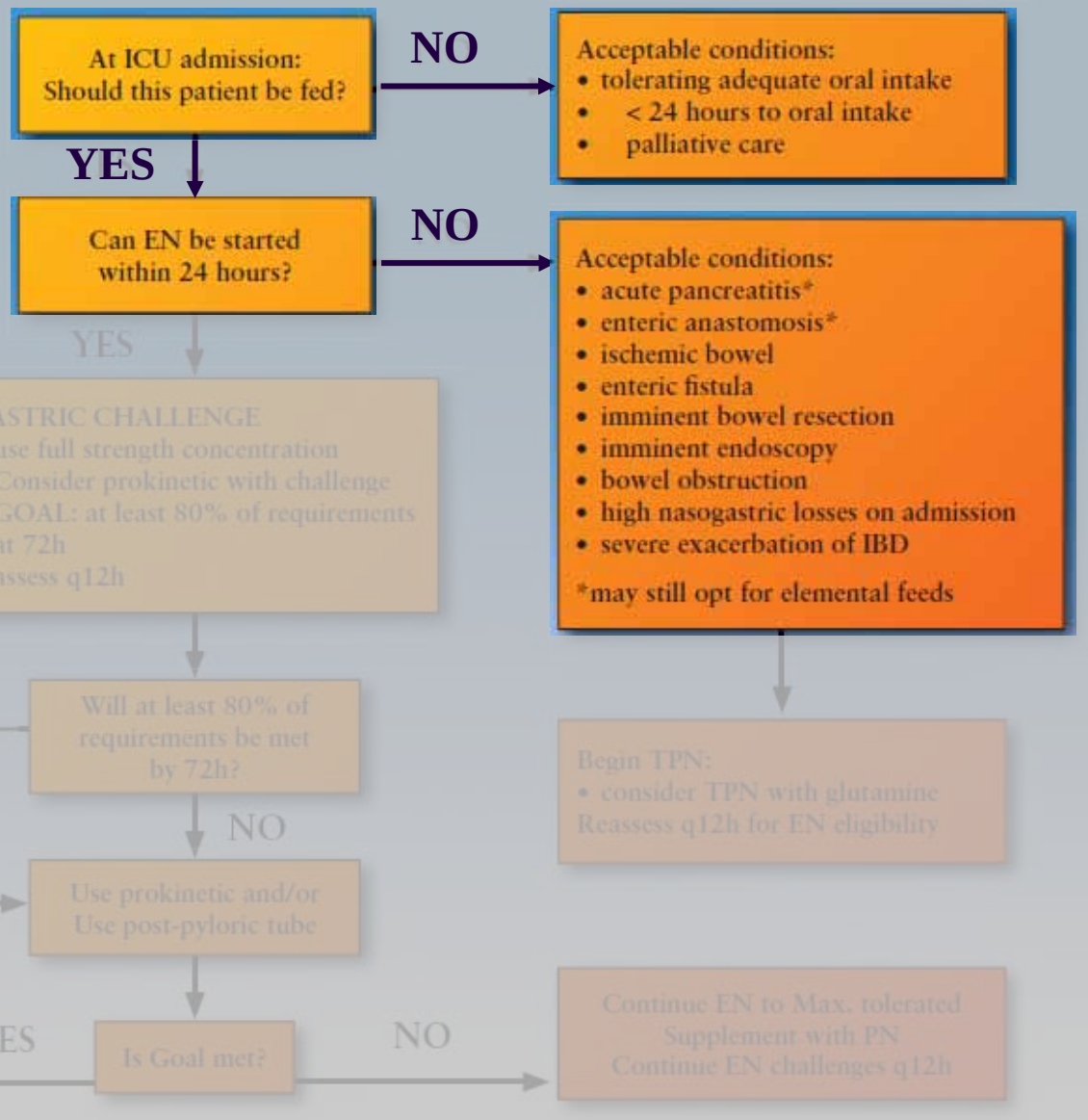

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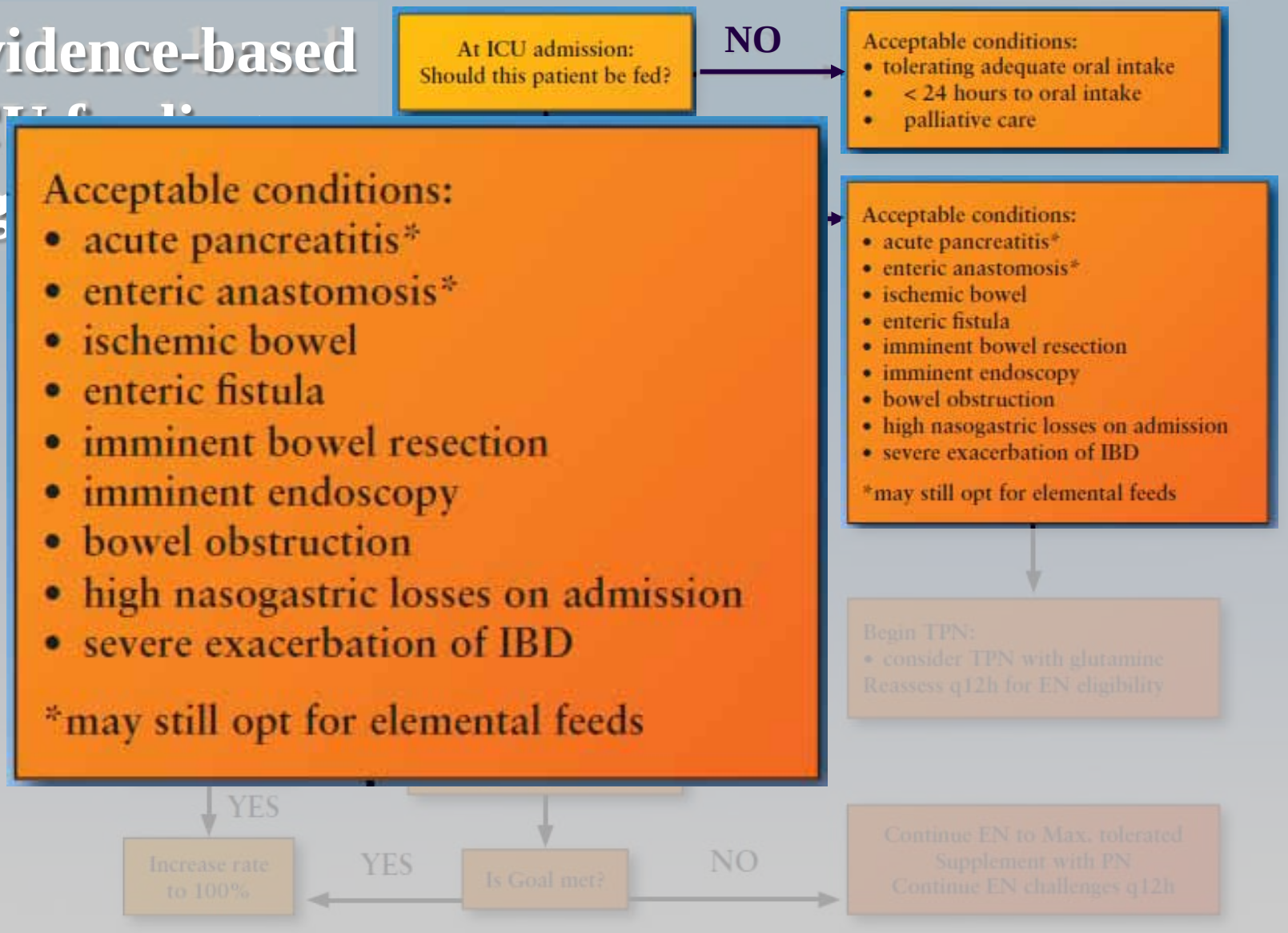

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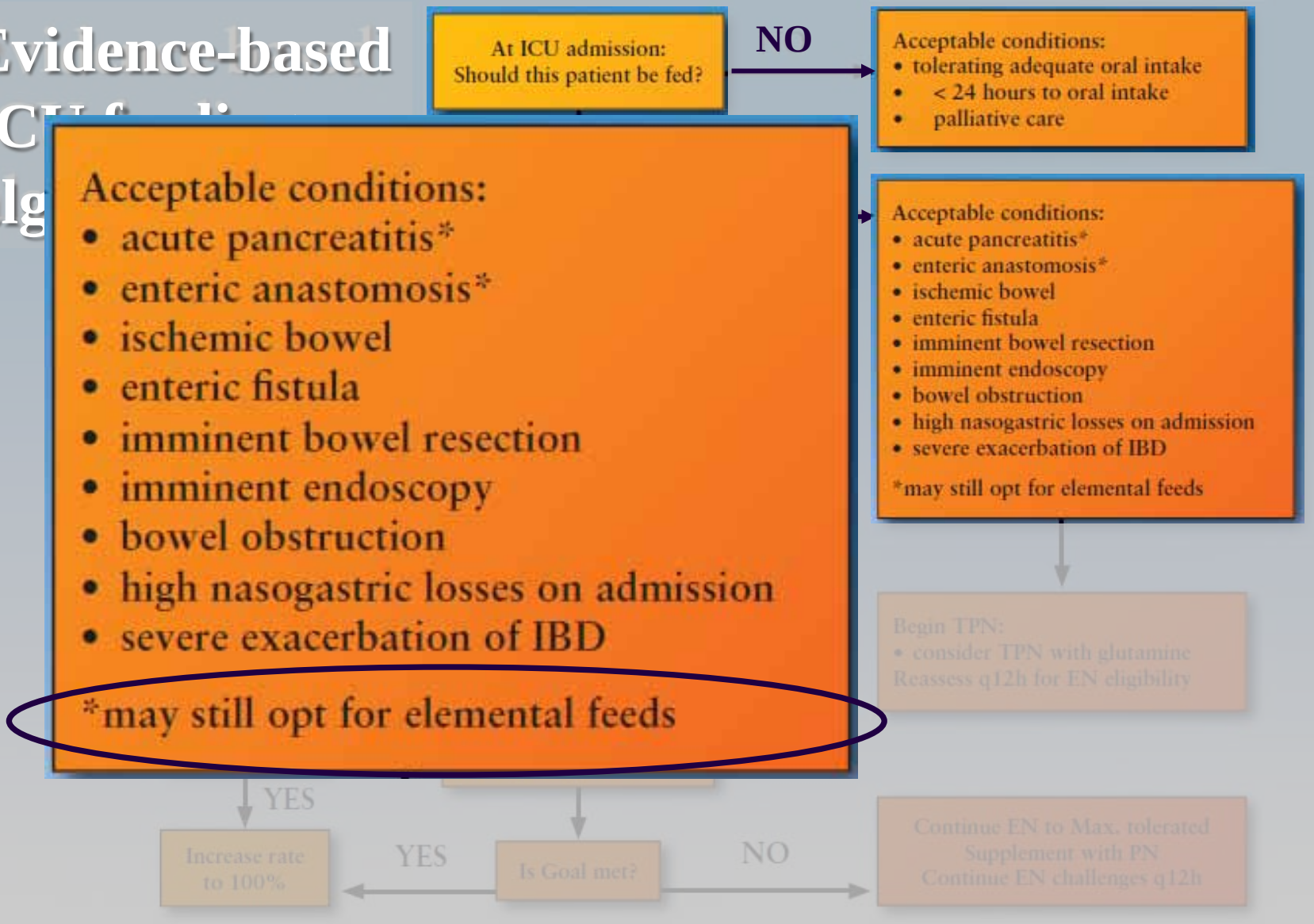

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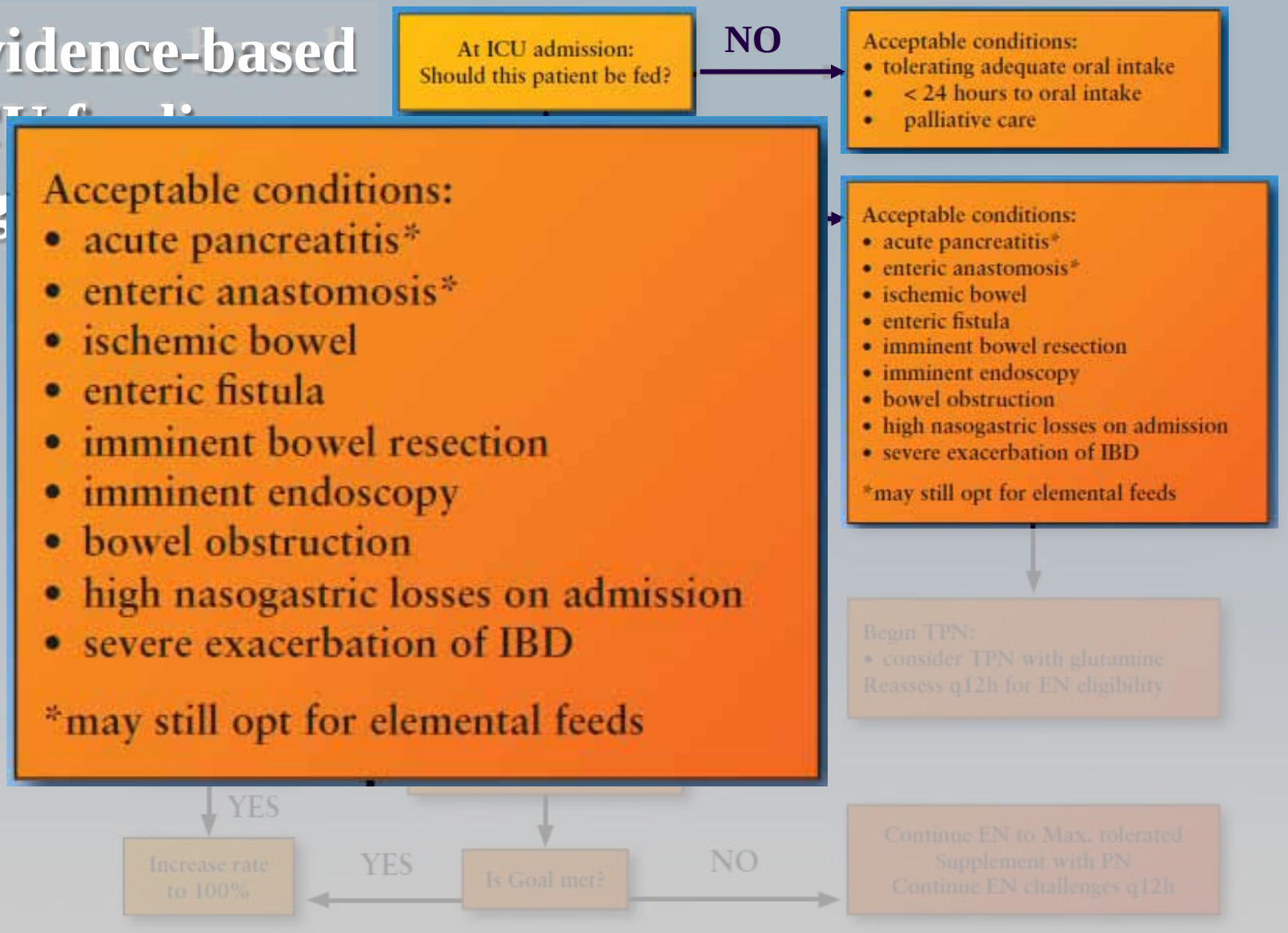

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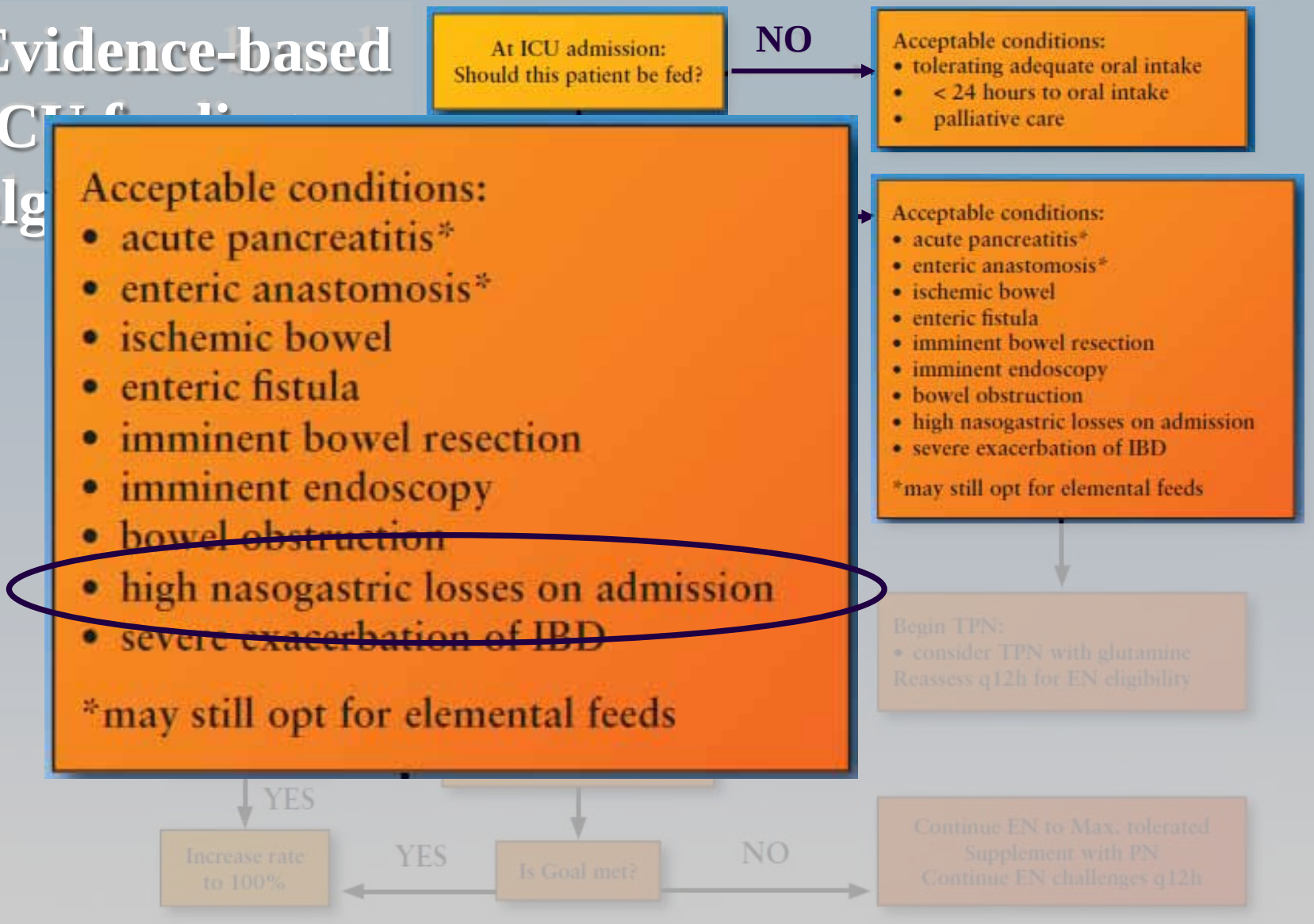

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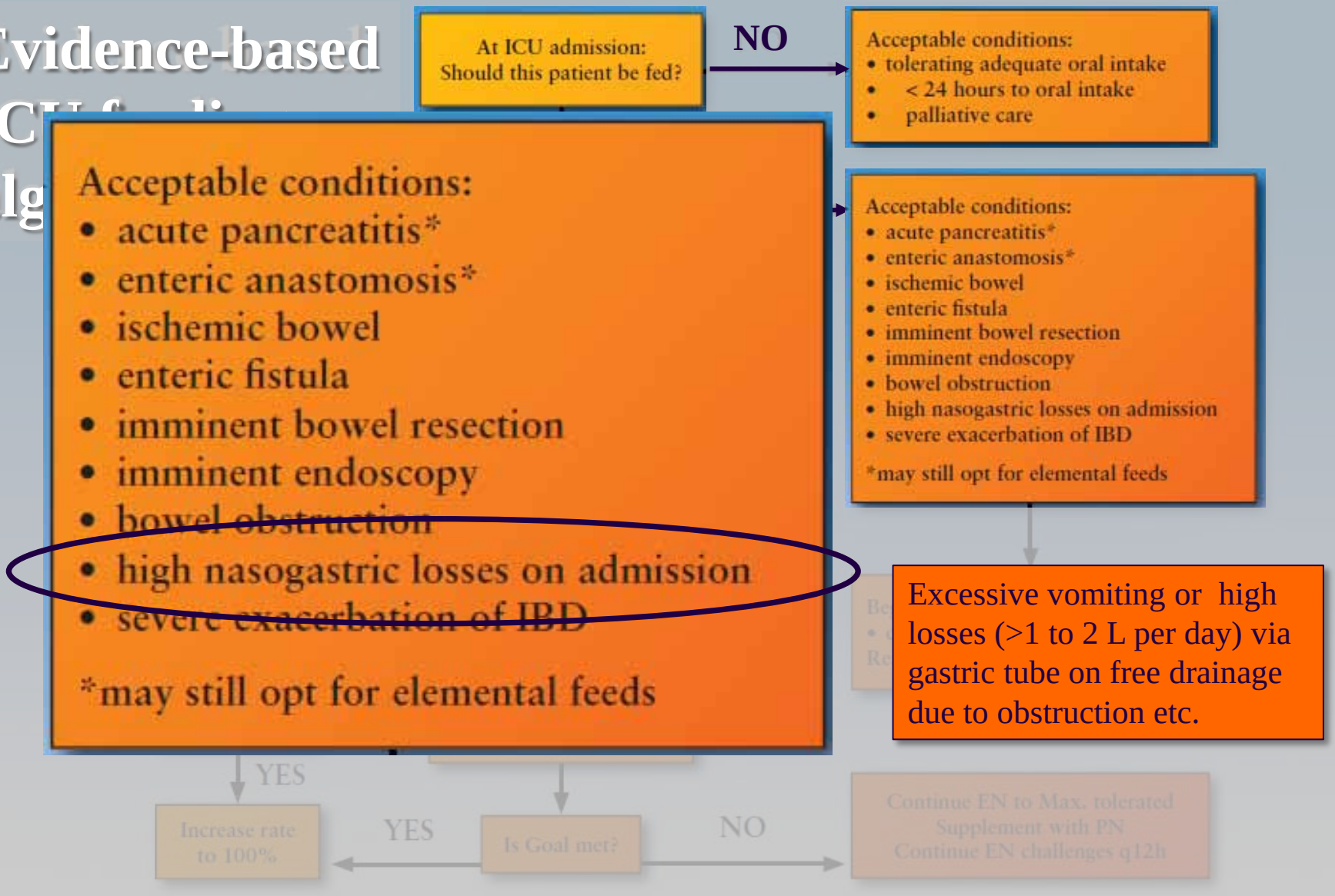

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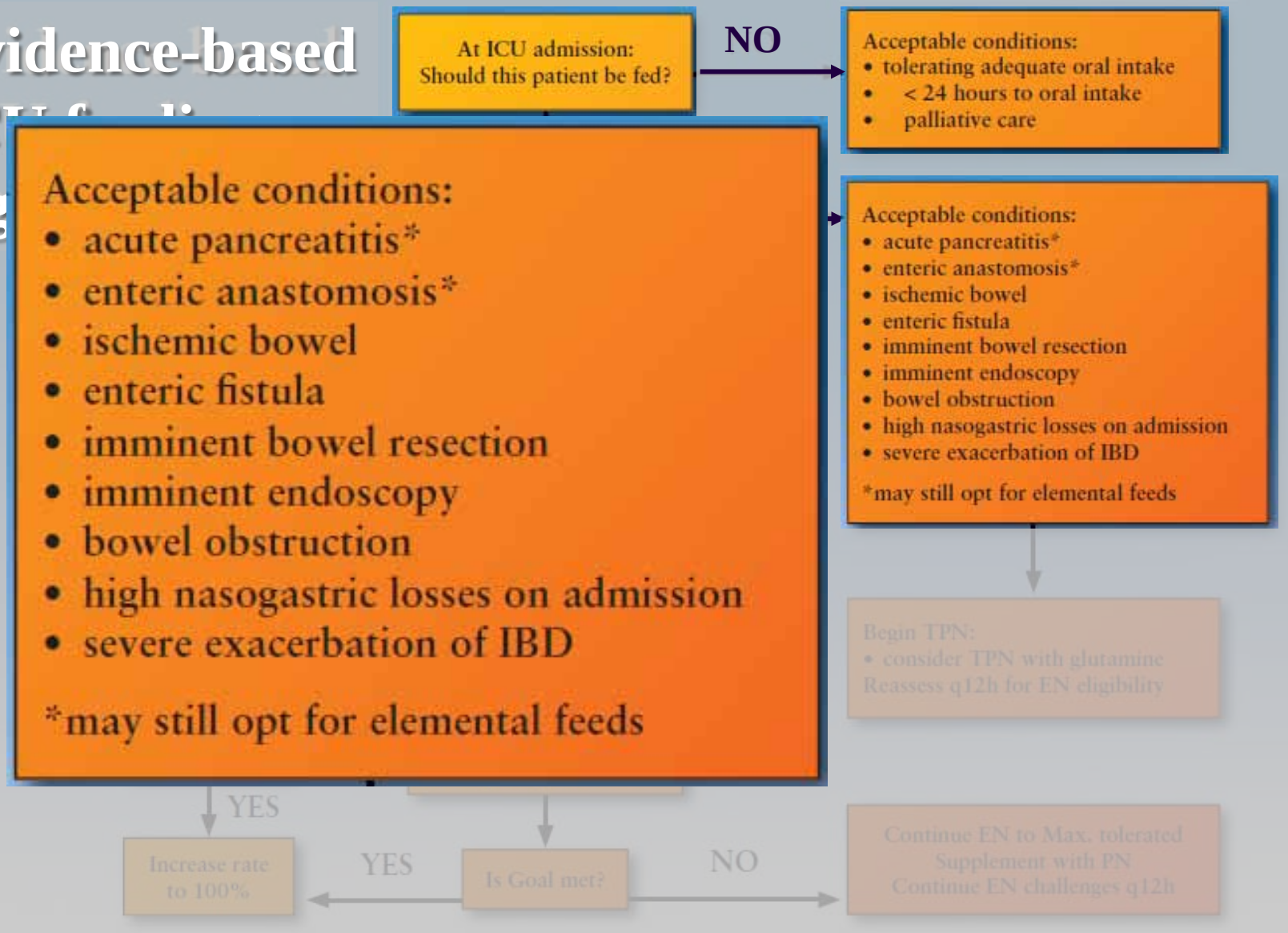

Gut Dysfunction

"The GI tract is not able to perform digestion and absorption adequately to satisfy the nutrient and fluid requirements of the body"

Blaser AR, Malbrain MLNG, Starkopf J et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. *Intensive Care Med* **2012**;38:384-394.

Gut Dysfunction

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- high gastric residuals
- vomiting
- diarrhoea
- paralytic ileus

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Evidence supporting ANZ Guideline recommendation

Intensive Care Med (2009) 35:2018–2027
DOI 10.1007/s00134-009-1664-4

SYSTEMATIC REVIEW

Gordon S. Doig
Philippa T. Heighes
Fiona Simpson
Elizabeth A. Sweetman
Andrew R. Davies

Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials

Doig GS, Heighes PT, Simpson F, Sweetman EA and Davies AR. Enteral nutrition within 24 h of ICU admission significantly reduces mortality: A meta-analysis of RCTs. *Intensive Care Medicine* **2009** Dec;35(Issue 12):2018-2027.

Methods

Comprehensive Literature search

- MEDLINE (http://www.PubMed.org) and EMBASE (http://www.EMBASE.com)
- Academic and industry experts were contacted,
- Reference lists of identified systematic reviews and evidence-based guidelines were hand searched by at least two authors.
- The search was not restricted by Language.

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Primary analysis

- Included only methodologically sound RCTs.

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Primary analysis

- Included only methodologically sound RCTs.

Primary outcome

- clinically meaningful patient oriented outcomes: (mortality / physical function / quality of life)

Secondary outcomes reported:

- vomiting/regurgitation, pneumonia, bacteraemia, sepsis and MODS.

Primary electronic search identified Abstracts (N = 4,800)

Potentially relevant papers identified and retrieved (N = 675)

Papers excluded, with reasons (N = 170)
Not RCTs (Letters, observational studies, systematic reviews, narrative reviews, previous meta-analyses)

RCTs identified for detailed evaluation (N = 505)

RCTs excluded, with reasons (N = 475)
329 Did not provide a primary comparison of timing of EN (includes 5 pseudo-randomised trials + 99 trials not reporting clinically meaningful outcomes)
72 Not adult critically ill population
46 Not primary nutritional support intervention (GH etc)
16 Cross-over trials
13 Pre-operative interventions

RCTs evaluating timing of EN (N = 30)

Excluded RCTs(N = 24)
7 - Early EN not started within 24 h of injury or ICU admission
4 - Patient oriented outcomes not reported (no mortality etc)
5 - Not critically ill patient population
2 - Early post-op oral intake, not early EN
2 - EN commenced at same time in both groups
1 - Immuno-enhanced EN (Impact)
2 - Excessive loss to follow-up
1 - Subgroup from a larger trial

Included in primary analysis (N = 6)

On topic, included in primary analysis

Chiarelli, 1990: 20 pts, burns

Kompan, 1999: 36 pts, trauma

Kompan, 2004: 52 pts, trauma

Nguyen, 2008: 28 pts, med/surg critically ill

Chuntrasakul, 1996: 38 pts, trauma

Pupelis, 2001: 60 pts, severe pancreatitis and peritonitis

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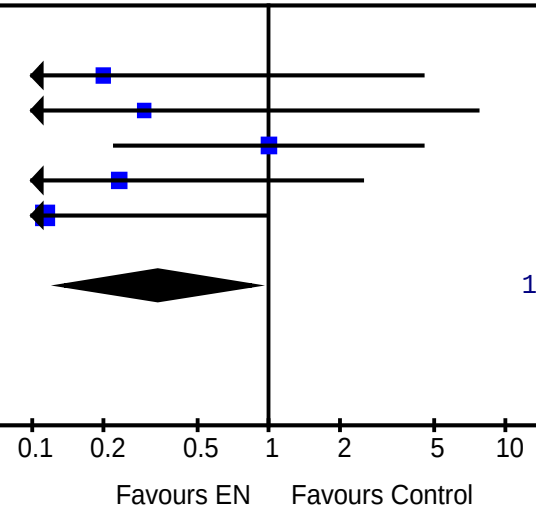
None of these trial excluded patients with pre-existing GI dysfunction.

Results: Primary MA, mortality

Review: Early EN (<24h) vs Control (Primary Analysis)
Comparison: 01 early EN vs Control
Outcome: 01 Mortality, Intention to treat analysis

Study or sub-category	early EN (<24 h) n/N	Control n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Chiarelli 1990	0/10	0/10			Not estimable
Kompan 1999	0/17	2/19		13.40	0.20 [0.01, 4.47]
Kompan 2004	0/27	1/25		8.89	0.30 [0.01, 7.63]
Nguyen 2008	6/14	6/14		19.95	1.00 [0.22, 4.47]
Chuntrasakul 1996	1/21	3/17		18.38	0.23 [0.02, 2.48]
Pupelis 2001	1/30	7/30		39.38	0.11 [0.01, 0.99]
Total (95% CI)	119	115		100.00	0.34 [0.14, 0.85]

Total events: 8 (early EN (<24 h)), 19 (Control)
Test for heterogeneity: Chi² = 3.20, df = 4 (P = 0.52), I² = 0%
Test for overall effect: Z = 2.31 (P = 0.02)



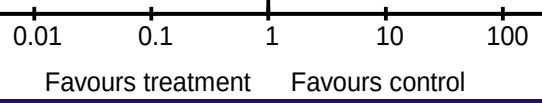
- Significant reduction in mortality with early EN (10% absolute reduction, P=0.02)

Results: Primary MA, Pneumonia

Review: Early EN (<24h) vs Control (Primary Analysis)
Comparison: 01 early EN vs Control
Outcome: 02 Pneumonia, Intention to treat analysis

Study or sub-category	early EN (<24 h) n/N	Control n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Kompan 2004	9/27	16/25		70.15	0.28 [0.09, 0.88]
Nguyen 2008	3/14	6/14		29.85	0.36 [0.07, 1.91]
Total (95% CI)	41	39		100.00	0.31 [0.12, 0.78]

Total events: 12 (early EN (<24 h)), 22 (Control)
Test for heterogeneity: Chi² = 0.06, df = 1 (P = 0.80), I² = 0%
Test for overall effect: Z = 2.47 (P = 0.01)



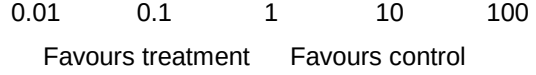
- Significant reduction in pneumonia with early EN (27% absolute reduction, P=0.01)

Results: Primary MA, MODS

Review: Early EN (<24h) vs Standard Care (Primary Anal - delayed EN)
Comparison: 01 early EN vs Control
Outcome: 03 Incidence of MODS, Intention to treat analysis

Study or sub-category	Treatment n/N	Control n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Kompan 1999	12/17	13/19		34.03	1.11 [0.27, 4.60]
Pupelis 2001	20/30	21/30		65.97	0.86 [0.29, 2.55]
Total (95% CI)	47	49		100.00	0.94 [0.40, 2.23]

Total events: 32 (Treatment), 34 (Control)
Test for heterogeneity: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%
Test for overall effect: Z = 0.13 (P = 0.89)



- No difference in *incidence* of MODS (68% vs 69% of patients, P=0.78)
- One trial reported a reduction in the *severity* of MODS (2.5 vs 3.1 organs failed per patient, P=0.057)

Summary

- Evidence supporting the presence of a significant mortality benefit from the provision of early EN (< 24 h of injury or ICU admission) has been present in our literature since 2003.

Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN* **2003**;27(5):355-373.

Summary

- Evidence supporting the presence of a significant mortality benefit from the provision of early EN (< 24 h of injury or ICU admission) has been present in our literature since 2003.
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- *Outcomes evaluating GI dysfunction not reported in our published systematic review…*

Doig GS, Heighes PT, Simpson F, Sweetman EA and Davies AR. Enteral nutrition within 24 h of ICU admission significantly reduces mortality: A meta-analysis of RCTs. *Intensive Care Medicine* **2009** Dec;35(Issue 12):2018-2027.

Measures of gut dysfunction

.... three trials did report measures of gut dysfunction:

Pupelis G, Selga G, Austrums E and Kaminski A. Jujenal feeding, even when instituted late, improves outcomes in patients with severe pancreatitis and peritonitis. *Nutrition* **2001**;17:91-94.

Chiarelli A, Enzi G, Casadei A, Baggio B, Balerio A and Mazzoleni F. Very early nutrition supplementation in burned patients. *Am J Clin Nutr* **1990**;51:1035-9.

Kompan L, Bidmar G, Spindler-Vesel A and Pecar J. Is early enteral nutrition a risk factor for gastric intolerance and pneumonia ? *Clin Nutr* **2004**;23:527-532.

Measures of gut dysfunction

Post-operative ileus:

- 6.7% (2/30) early EN vs. 20% (6/30) delayed, p=0.25

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Toxic ileus:

- 10% (1/10) early EN vs. 0% (0/10) delayed, p=0.6

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Upper Digestive Intolerance:

- GRV > 200mls on two consecutive occasions or vomiting

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Upper Digestive Intolerance:

- GRV > 200mls on two consecutive occasions or vomiting
- 70% (19/27) early EN vs. 80% (20/25) delayed, p=0.52

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UDI lasted significantly longer in delayed EN patients:

- 1.0 ± 0.9 days vs. 2.2 ± 2.7 days, p =0.045

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Novel MA of gut dysfunction

Review: Early EN (<24h) vs Standard Care
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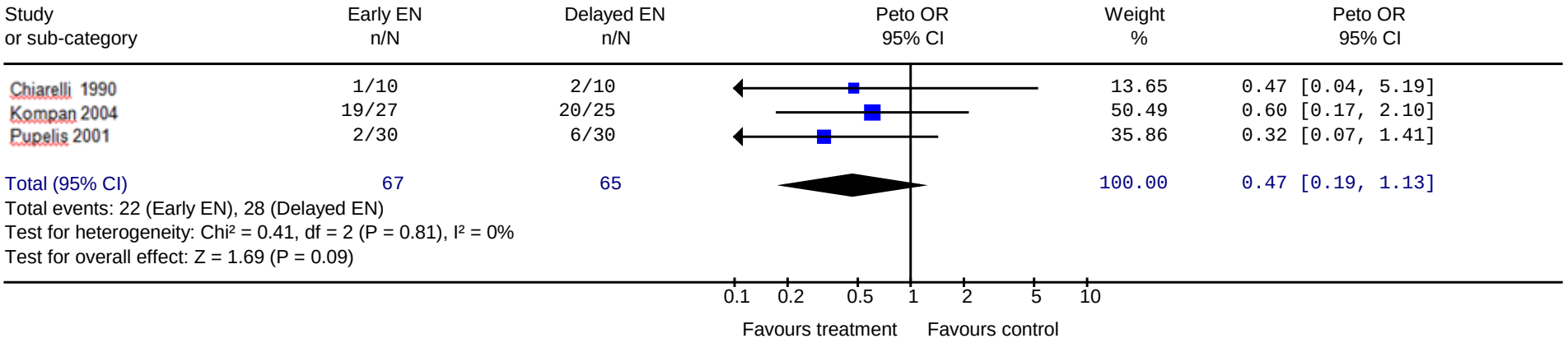
Outcome: 03 Complications (Gut Dysfunction)



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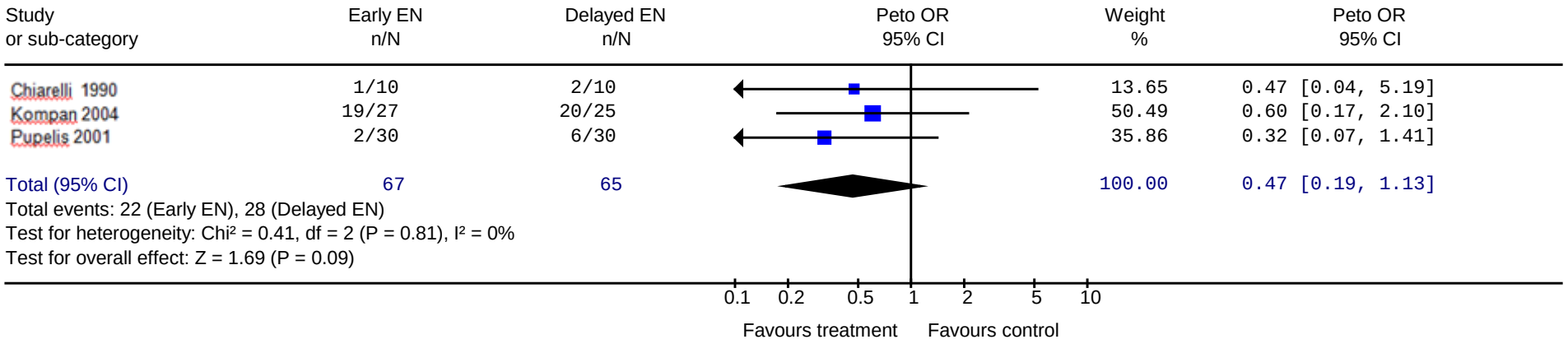

- Meta-analysis suggests the provision of early EN *may* reduce the incidence of gut dysfunction:

  33% (22/67) of patients vs. 43% (28/65) of patients, p=0.09, no heterogeneity
- One included trial demonstrated a significantly shorter duration of gut dysfunction (p=0.045)

In Summary

- Evidence supporting the presence of a significant mortality benefit from the provision of early EN (< 24 h of injury or ICU admission) has been present in our literature since 2003.
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ANZ Guideline recommends early EN. Recommendation does not specifically exclude patients with pre-existing GI dysfunction.

Doig GS, Heighes PT, Simpson F, Sweetman EA and Davies AR. Enteral nutrition within 24 h of ICU admission significantly reduces mortality: A meta-analysis of RCTs. *Intensive Care Medicine* 2009 Dec;35(Issue 12):2018-2027.

Effect of Evidence-Based Feeding Guidelines on Mortality of Critically Ill Adults

A Cluster Randomized Controlled Trial

CARING FOR THE CRITICALLY ILL PATIENT

JAMA, December 17, 2008—Vol 300, No. 23

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Table 5. Secondary Outcomes and Concomitant Therapies

Mean Events	Value (95% CI)			*P* Value[c]
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Secondary outcomes				
Witnessed aspiration (patients receiving EN), events/1000 fed patient-days	2.19 (1.18 to 4.08)	4.33 (2.33 to 8.05)	−2.14 (−3.69 to 3.26)	.28

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Questions?

Immediately after resuscitation:

Stable shock can be defined as:

Shock Index ≤ 1 (heart rate ÷ systolic blood pressure = Shock Index)

or

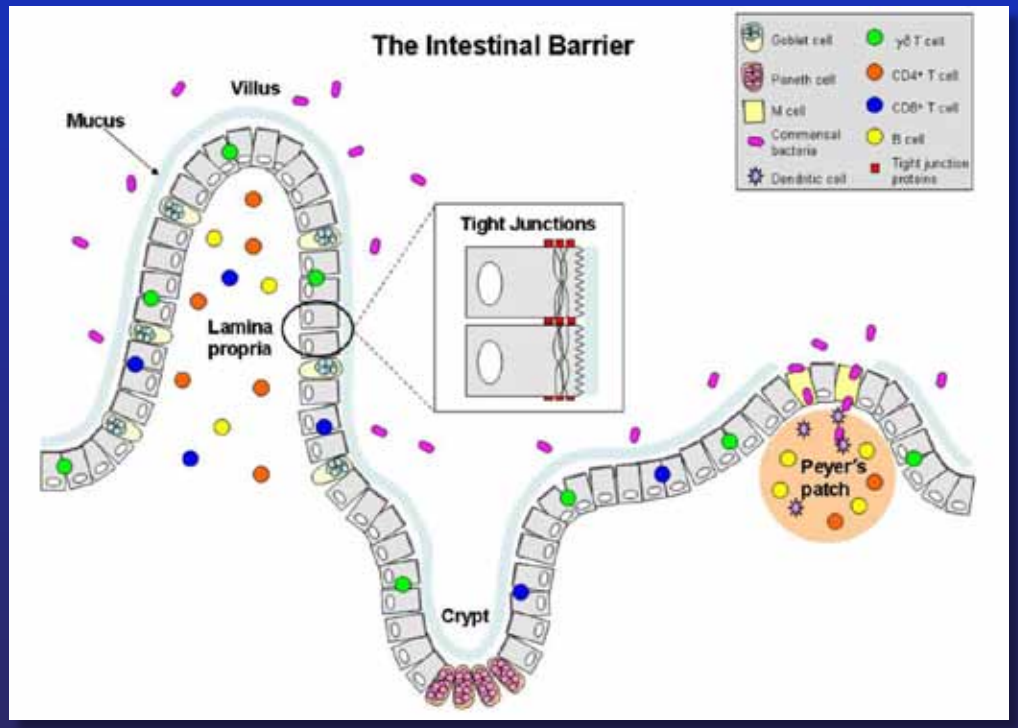
Systolic blood pressure > 90 mmHg **or** mean blood pressure > 70 mmHg for at least one hour.

Doig GS and Heighes PT. A Change Management Perspective on a Novel Meta-Analysis: Early Enteral Nutrition in Trauma Patients. *ICU Management Forum*, 2011;11(3):26-29.

The gut as the motor of MODs

With the onset of critical illness:

- Loss of functional and structural integrity of the intestinal epithelium.



Clark JA and Coopersmith CM. Intestinal crosstalk – a new paradigm for understanding the gut as the "motor" of critical illness. *Shock* 2007;28(4):384-393.

Detailed reasons for trial exclusion from our MA

Trial Name	Reasons for exclusion	DH MA
Eyer 1993	**1.** Excessive ltf: **27%** (14/52 pts ltf, missing) **2.** Early EN not started within 24 h of injury or ICU admit (Early EN average time **31 hours**)	Ö
Minard 2000	**1.** Early EN not started within 24 h of injury or ICU admit (Early EN defined as within 60 hours, average time **33 h**) **2.** Patients received immune-enhanced EN (Impact), not standard EN	Ö
Singh 1998	**1.** Not conducted in a critically ill patient population **2.** Early EN not started within 24 hours of injury or ICU (EN begun 24 – 48 post-op)	Ö
Ibrahim 2002	**1.** Enteral nutrition commenced at the same time in both groups (Early full goal feeding versus early restricted) **2.** Pseudo randomised	
Schroeder 1991	**1.** No patient oriented outcomes	
Hasse 1995	**1.** No patient oriented outcomes	
Watters 1997	**1.** No patient oriented outcomes	
Seri 1984	**1.** Not conducted in a critically ill patient population **2.** No patient oriented outcomes (No deaths reported as of study day 7, no outcomes reported beyond day 7)	
Taylor 1999	**1.** Enteral nutrition commenced at the same time in both groups (Gastric versus post-pyloric feeding)	
Sagar 1979	**1.** No patient oriented outcomes	
Beier-Holgersen 1996	**1.** Not conducted in a critically ill patient population **2.** Early post-op oral intake, not early EN	
Carr 1996	**1.** Not conducted in a critically ill patient population (elective intestinal resection)	
Heslin 1997	**1.** Not conducted in a critically ill patient population **2.** Patients received immune-enhanced EN (Impact), not standard EN	
Schilder 1997	**1.** Not conducted in a critically ill patient population **2.** Early post-op oral intake, not early EN **3.** Pseudo-randomised	
Grahm 1989	**1.** Early EN not started within 24 h of injury or ICU admit (commenced within **36 hours**) **2.** Pseudo-randomised	