5.2 Strategies to Optimize Delivery and Minimize risks of EN: Motility agents January 31st 2009

Recommendation:

Based on 1 level 1 study and 5 level 2 studies, in critically ill patients who experience feed intolerance (high gastric residuals, emesis), we recommend the use of a promotility agent. Given the safety concerns associated with erythromycin, the recommendation is made for metoclopramide. There are insufficient data to make a recommendation about the use of combined use of metoclopramide and erythromycin.

Discussion: Subsequent to an earlier systematic review that looked primarily at the effects of motility agents on gastric emptying and feed intolerance (1), additional randomized trials that report on clinical outcomes have been published. We have focused on those studies that report clinical outcomes (mortality, infection, length of stay) as well as evaluate the impact of motility agents on measures of nutritional adequacy. Recent data from a non-randomized observational study showed that ICU patients with high gastric residual volumes have delayed gastric emptying and that by initiating prokinetic therapy, this accelerates gastric emptying to resemble that of patients tolerating EN (2). The committee noted the lack of treatment effect on clinical outcomes from these trials, however the beneficial effects of motility agents on feed intolerance and nutritional adequacy were recognized and thought to be important. In five out of the six trials, motility agents were associated with a significant improvement in nutritional intake. Due to the concerns re: bacterial resistance, the potential for cardiac toxicity and tachyphylaxis with the use of erythromycin and the uncertainty around the safety and efficacy of naloxone as a motility agent, it was agreed that the recommendation be made for metoclopramide. Given the low probability of harm, the favourable feasibility and cost considerations and the benefits of motility agents in improving nutrient intake, particularly when initiating early EN, the committee decided that motility agents be considered as a strategy to optimize nutrient intake.

(1) Booth CM, Heyland DK, Paterson WG. Gastrointestinal promotility drugs in the critical care setting: a systematic review of the evidence. Crit Care Med. 2002 Jul;30(7):1429-35

(2) Landzinski James et al .Gastric motility function in critically ill patients tolerant vs. intolerant to gastric nutrition. JPEN 2008;32:45-50,2008.

	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	2 (nutrition adequacy)
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	2
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 outcomes—a higher score indicates presence of more of these features in the trials appraised	2
Homogeneity or Reproducibility	Similar direction of findings among trials—a higher score indicates greater similarity of direction of findings among trials	3
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)	3

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.	1
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	3
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listed—a higher score indicates a lower probability of harm	2

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Question: Compared to standard practice (placebo), does the routine use of motility agents improve clinical outcomes in critically ill patients?

Summary of Evidence: There was one systematic review that reported on surrogate outcomes such as gastric emptying and feed intolerance (Booth et al 2002) and 4 level 2 studies and 1 level 1 study that reported on clinical outcomes. In addition, there were 1 level 1 and 3 level 2 studies that reported on nutritional endpoints. Of the total of 9 studies included, 6 studies looked at the use of a single motility agent compared to placebo. Of these, 3 studies compared erythromycin to placebo (Chapman 2000, Berne 2002, Reigner 2002), 2 compared metoclopramide to placebo (Yavagal 2000 and Nursal 2007) and an earlier study compared the use of enteral naloxone to placebo (Meissner 2003). The data from three additional studies was not included in the meta-analysis as the interventions varied (MacLaren 2008 erythromycin vs. metoclopramide; Nguyen 2007 erthryomycin plus metoclopramide vs. erythromycin alone; Biovin 2001 erythromycin vs. small bowel feeding) (Nguyen 2007). Given the uncertainty around the safety and efficacy of naloxone as a motility agent, the data from the Meissner 2003 study was not included.

Mortality: When the data from the five studies of metoclopramide and erythromycin alone were aggregated, the use of motility agents had no effect on mortality (RR = 1.03, 95% CI 0.85, 1.26, p =0.75, no heterogeneity present) (figure 1).

Infections: In the one study using naloxone, there was a significant reduction in pneumonia (Meissner 2003) and in the other study, metoclopramide had no effect on the incidence of pneumonia (Yavagal 2000). One study reported on the number of infections per group rather than the number of patients with infections and again there were no differences between the two groups (Berne 2002).

LOS, Ventilator days: There were no differences between the groups in the 3 studies that reported on these outcomes (Meissner 2003, Nursal 2007 and Nguyen 2007).

Other: The time to development of pneumonia was statistically different in the one study (Yavagal) (5.95 days versus 4.46 days, p=0.006), however, the clinical significance of this difference is negligible. All studies demonstrated positive effects on nutrition indices i.e. lower gastric residual volumes, fewer interruptions in feeds, higher % feeds tolerated, fewer days to target calories, with the exception of 2 studies (Boivin 2001, Nursal 2007) in which there were no significant differences seen. The combined approach of erythromycin plus metoclopramide resulted in a significant higher calorie intake, lower gastric residual volumes and lower need for post pyloric feeds (Nursal 2007).

Conclusion:

1) Motility agents have no effect on mortality or infectious complications in critically ill patients.
2) Motility agents may be associated with an increase in gastric emptying, a reduction in feeding intolerance and a greater caloric intake in critically ill patients.

Level 1 study: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.
Level 2 study: If any one of the above characteristics are unfulfilled.

Table 1. Randomized Studies Motility Agents In Critically Ill Patients

Study	Population	Methods (score)	Intervention	Mortality # (%)† Experimental	Control	Infections # (%)‡ Experimental	Control	Nutritional Indices Experimental	Control
Placebo-controlled trials									
1) Chapman 2000	Mixed ICU patient with GRV>250ml N=20	C.Random: Yes ITT: yes Blinding: Yes (12)	Erythro 200 mg IV vs placebo x 1 dose	NR	NR	NR	NR	Successful feeding defined as GRV <250 mo and continuing with feeds. Erythro 9/10 vs placebo 5/10, p=0.05	
2) Yavagal 2000	Mixed ICU N = 305	C.Random: not sure ITT: yes Blinding: yes (10)	Metoclopramide 10 mg NG q 6 h vs. placebo	73/ 131 (56)	92/174 (53)	Pneumonia 22/131 (17)	Pneumonia 24/174 (14)	NR	NR
3) Berne 2002	Critically injured patients n= 48	C.Random: not sure ITT: no Blinding: no (6)	Erythromycin 250 mg IV q 6 hrs vs. placebo	2/32 (6)	2/36 (6)	pneumonia 13/32 per group*	pneumonia 18/36 per group*	Feeds tolerated at 48 hrs 58 % 44 %,p=0.001 Feeds tolerated for the study 65 % 59%, p=0.06	
4) Reignier 2002	Mixed ICU patients N = 48	C.Random: not sure ITT: yes Blinding: no (6)	Erythro 250 mg q 6h IV vs placebo x 5 days	6/20 (30)	8/20 (40)	NR	NR	EN discontinued if GRV>250 or vomited: Erythro 35% vs placebo 70%, p<0.001	
5) Meissner** 2003	ICU patients N =84	C.Random: yes ITT: no Blinding: double (11)	Naloxone 8 mg q 6 hrs via NG vs, placebo	6/38 (16)	7/43 (16)	Pneumonia 13/38 (34)	Pneumonia 24/43 (56)	Feeding volumes after day 3 Higher in naloxone group (trend) Amount of Reflux (mls) 54 129	
6) Nursal 2007	Traumatic Brain Injured patients N = 19	C.Random: no ITT: no Blinding: double (10)	Metoclopramide 10 mg IV TID vs. saline IV TID	Hospital 3/10 (30)	Hospital 3/9 (33)	NR	NR	Patients with high GRV 5/10 (50) 2/9 (22) Days to target calories 5.8 ± 5.2 3.4 ± 1.4 Calorie intake/total calories 61.3% 92.2%	

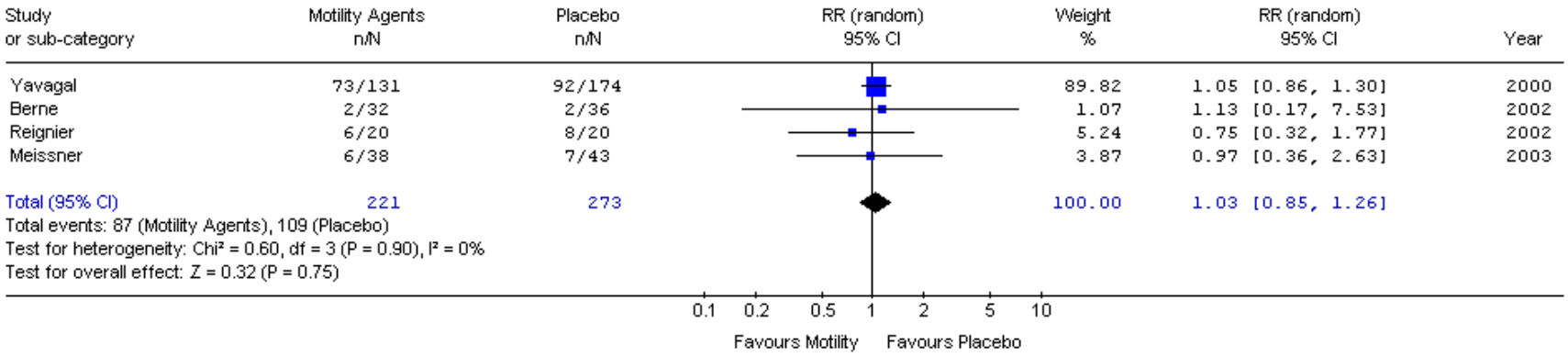
Head to Head Comparisons								
7) MacLaren 2008	Mixed ICU patient with GRV>150ml N=20	C.Random: not sure ITT: yes Blinding: no (9)	Erythro 250 mg q6h vs Meto 10 mg IV q 6h for 4 doses	NR	NR	NR	NR	Both agents resulted in significant reduction in GRV and increase in feeding rate
Combo vs Mono								
8) Nguyen 2007	Mixed ICU patients N = 75	C.Random: yes ITT: yes Blinding: double (11)	Combination of Erythromycin 200 mg IV bid + Metoclopramide 10 mg IV qid vs. Erythromycin 200 mg IV bid alone	Hospital 8/37 (22)	Hospital 10/38 (26)	NR	NR	Failure of feeding (days) 6.5 ± 0.5 4.5 ± 0.5 Caloric intake % prescribed 7 days Higher in combination group (p=0.02) Gastric residual volumes Lower in combination group (p<0.05) Need for post-pyloric feeds 2/37 (5) 8/38 (21)
Motility agent vs Small bowel tubes								
9) Boivin 2001	Mixed ICU patients (80)	C.Random: not sure ITT: no Blinding: no (5)	Erythro 200 mg q 8 hrs x 96 hrs vs transpyloric feeding	7/39 (18)	7/39 (18)	NR	NR	No difference in time to goal rate or overall adequacy.

* infections reported as per group, not # patients with infections

**data from this study not included in the meta-analysis due to the uncertainty around the safety and efficacy of naloxone as a motility agent.

Figure 1.

Review: Motility Agents
Comparison: 01 Motility Agents vs. Placebo
Outcome: 02 Mortality



TOPIC: 5.2. Motility Agents

Article inclusion log

Criteria for study selection

Type of study: RCT or Meta-analysis
Population: Critically ill, ventilated patients (no elective surgery patients)
Intervention: Motility agents (exclude Cisapride)
Outcomes: Mortality, LOS, QOL, functional recovery, complications, and measures of nutritional adequacy. Exclude if just report measures of gastric emptying.

	Author	Journal	I	E	Why Rejected
1	Dive	Crit Care Med 1995		√	Crossover design
2	Spapen	Crit Care Med 1995		√	Cisapride
3	Heyland	Am J Respir Crit Care Med 1996		√	No clinical outcomes
4	Williams	Brit J Intensive Care 1996		√	Cisapride
5	Altomare	Br J Surgery 1997		√	Not critically ill
6	Goldhill	Crit Care Med 1998		√	Cisapride
7	Jooste	Intensive Care Med 1999		√	No clinical outcomes
8	Chapman	Crit Care Med 2000	√		
9	MacLaren	Crit Care Med 2000		√	Crossover design
10	Yavagal	Crit Care Med 2000	√		
11	Boivin	Crit Care Med 2001	√		
12	Van der Spoel	Intensive Care Med 2001		√	Neostigmine
13	Berne	J Trauma 2002	√		
14	Booth*	Crit Care Med 2002		√	Systematic review, individual studies looked at
15	Reigner	Crit Care Med 2002	√		
16	Chapman	Intensive Care Medicine 2003		√	Crossover design
17	Griffith	Crit Care Med 2003		√	No clinical outcomes
18	Marino	Br J Neurosurg 2003		√	No clinical outcomes
19	Meissner	Crit Care Med 2003	√		
20	Ritz	Intensive Care Med 2005		√	No clinical outcomes
21	Sustic	Croat Med J 2005		√	No clinical outcomes
22	Nguyen	Crit Care Med 2007	√		
23	Nursal	J Clin Neurosci 2007	√		
24	MacLaren	JPEN J Parenter Enteral Nutr 2008	√		

I = included
E = excluded

References

1. Dive A, Miesse C, Galanti L, Jamart J, Evrard P, Gonzalez M, Installe E. Effect of erythromycin on gastric motility in mechanically ventilated critically ill patients : A double-blind, randomized, placebo-controlled study. Crit Care Med 1995;23(8):1356-1362.

2. Spapen HD, Duinslaeger L, Diltoer M, Gillet R, Bossuyt A, Huyghens L. Gastric emptying in critically ill patients is accelerated by adding cisapride to a standard enteral feeding protocol: Results of a prospective, randomized, controlled trial. Crit Care Med 1995;23(3):481-485.

3. Heyland DK, Tougas G, Cook DJ, Guyatt GH. Cisapride improves gastric emptying in mechanically ventilated, critically ill patients. Am J Respir Crit Care Med 1996;154:1678-1683.

4. Williams A. The effect of cisapride on gastric stasis in intensive care patients. Br J Intensive Care 1996;6:186-193.

5. Altomare DF, Rubini D, Pilot MA, Farese S, Rubini G, Rinaldi M, Memeo V, D'Addabbo A. Oral erythromycin improves gastrointestinal motility and transit after subtotal but not total gastrectomy for cancer. Br J Surg 1997;84:1017-1021.

6. Goldhill DR, Toner CC, Tarling MM, Baxter K, Withington PS, Whelpton R. Double-blind, randomized study of the effect of cisapride on gastric emptying in critically ill patients. Crit Care Med. 1997 Mar;25(3):447-51. Comment in: Crit Care Med. 1998 Jan;26(1):188-9.

7. Jooste CA, Mustoe J, Collee G. Metoclopramide improves gastric motility in critically ill patients. Intensive Care Med 1999;25:464-468.

8. Chapman MJ, Fraser RJ, Kluger MT, Buist MD, De Nichilo DJ. Erythromycin improves gastric emptying in critically ill patients intolerant of nasogastric feeding. Crit Care Med. 2000 Jul;28(7):2334-7. Comment in: Crit Care Med. 2000 Jul;28(7):2657-9.

9. MacLaren R, Kuhl DA, Gervasio JM, Brown RO, Dickerson RN, Livingston TN, Swift K, Headley S, Kudsk KA, Lima JJ. Sequential single doses of cisapride, erythromycin, and metoclopramide in critically ill patients intolerant to enteral nutrition: A randomized, placebo-controlled, crossover study. Crit Care Med 2000;28(2):438-444.

10. Yavagal DR, Karnad DR, Oak JL: Metoclopramide for preventing pneumonia in critically ill patients receiving enteral tube feeding: A randomized controlled trial. Crit Care Med 2000;May;28(5):1408-11.

11. Boivin MA, Levy H. Gastric feeding with erythromycin is equivalent to transpyloric feeding in the critically ill. Crit Care Med. 2001 Oct;29(10):1916-9.

12. van der Spoel JI, Oudemans-van Straaten HM, Stoutenbeek CP, Bosman RJ, Zandstra DF. Neostigmine resolves critical illness-related colonic ileus in intensive care patients with multiple organ failure--a prospective, double-blind, placebo-controlled trial. Intensive Care Med. 2001 May;27(5):822-7.

13. Berne JD, Norwood SH, McAuley CE, Vallina VL, Villareal D, Weston J, McClarty J. Erythromycin reduces delayed gastric emptying in critically ill trauma patients: a randomized, controlled trial. J Trauma. 2002 Sep; 53(3): 422-5.

14. Booth CM, Heyland DK, Paterson WG. Gastrointestinal promotility drugs in the critical care setting: A systematic review of the evidence. Crit Care Med 2002;Jul;30(7):1429-35.

15. Reignier J, Bensaid S, Perrin-Gachadoat D, Burdin M, Boiteau R, Tenaillon A.Erythromycin and early enteral nutrition in mechanically ventilated patients. Crit Care Med 2002;Jun; 30(6): 1237-41.

16. Chapman M, Fraser R, de Beaux I, Creed S, Finnis M, Butler R, Cmielewski P, Zacharkis B, Davidson G. Cefazolin does not accelerate gastric emptying in the critically ill. Intensive Care Med 2003;29:1169-1172.

17. Griffith DP, McNally AT, Battey CH, Forte SS, Cacciatore AM, Szeszycki EE,Bergman GF, Furr CE, Murphy FB, Galloway JR, Ziegler TR. Intravenous erythromycin facilitates bedside placement of postpyloric feeding tubes in critically ill adults: a double-blind, randomized, placebo-controlled study. Crit Care Med 2003 Jan; 31(1):39-44.

18. Marino LV, Kiratu EM, French S, Nathoo N. To determine the effect of metoclopramide on gastric emptying in severe head injuries: a prospective, randomized, controlled clinical trial. Br J Neurosurg 2003 Feb;17(1):24-8.

19. Meissner W, Dohrn B, Reinhart K. Enteral naloxone reduces gastric tube reflux and frequency of pneumonia in critical care patients during opioid analgesia. Crit Care Med 2003 Mar; 31(3):776-80.

20. Ritz MA, Chapman MJ, Fraser RJ, Finnis ME, Butler RN, Cmielewski P, Davidson GP, Rea D. Erythromycin dose of 70 mg accelerates gastric emptying as effectively as 200 mg in the critically ill. Intensive Care Med. 2005 Jul;31(7):949-54. Epub 2005 Jun 7.

21. Sustić A, Zelić M, Protić A, Zupan Z, Simić O, Desa K. Metoclopramide improves gastric but not gallbladder emptying in cardiac surgery patients with early intragastric enteral feeding: randomized controlled trial. Croat Med J. 2005 Apr;46(2):239-44.

22. Nguyen NQ, Chapman M, Fraser RJ, Bryant LK, Burgstad C, Holloway RH. Prokinetic therapy for feed intolerance in critical illness: One drug or two? Crit Care Med 2007;35(11):2561-2567.

23. Nursal TZ, Erdogan B, Noyan T, Cekinmez M, Atalay B, Bilgin. The effect of metoclopramide on gastric emptying in traumatic brain injury. J Clin Neurosurg 2007;14:344-348.

24. MacLaren R, Kiser TH, Fish DN, Wischmeyer PE. Erythromycin vs metoclopramide for facilitating gastric emptying and tolerance to intragastric nutrition in critically ill patients. JPEN J Parenter Enteral Nutr 2008;32(4):412-419.