

Erythromycin is more effective than metoclopramide in the treatment of feed intolerance in critical illness

In intensive care patients with feed intolerance, erythromycin reduces gastric residual volume more effectively than metoclopramide (NNT 4). Both drugs rapidly become ineffective. In patients who fail monotherapy, an open-label, non-controlled extension of this study suggests combination therapy may be effective.

Level of evidence: 1⁺ (RCT with a low risk of bias)

Appraised by: Kate Janossy

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Three-part clinical question:

Patients: Mechanically ventilated intensive care patients with feed intolerance.

Intervention: Erythromycin or metoclopramide.

Outcome: Feed tolerance.

Search terms: Ovid Medline MeSH terms: enteral nutrition; gastrointestinal agents; critical illness.

The study: Double-blinded concealed randomised controlled trial but without intention-to-treat. Patients randomised to either metoclopramide or erythromycin. Feeding recommenced at 40 mL/h after the first dose of trial drug. Stomach aspirated two hours after first dose then six hourly. If GRV <250 mL the feeding rate was increased by 20 mL/h every six hours up to predicted requirement. Therapy continued for seven days or until discharge in feed-tolerant patients. Patients who failed with either erythromycin or metoclopramide were treated with open-label combination therapy.

The study patients:

Inclusion criteria: Mechanically ventilated patients in a mixed

medical and surgical intensive care unit, who failed nasogastric feeding (six hourly gastric residual volume >250 mL, >6 h after starting enteral feeding at >40 mL/h).

Main exclusion criteria: Recent administration of or contraindication to prokinetics, major abdominal surgery or suspected obstruction or perforation. Seventeen of the 107 patients enrolled were excluded from the analysis because their participation in the trial was <7 days (as per trial protocol), nine due to early recovery and tolerance of oral diet and eight due to death from withdrawal of medical therapy.

Demographics similar in the two groups in most respects: Admission APACHE II 25, 73% male, BMI 27, six days in ICU before randomisation, pre-treatment gastric residual volume (GRV), feeding rate achieved before development of feed intolerance, blood glucose, medication and ventilation rates. However, there were significantly more septic patients in the erythromycin group and trauma patients in the metoclopramide group.

Erythromycin group (N=53; 45 analysed): 200 mg IV twice daily. Placebo IV, twice daily.

Metoclopramide group (N=54; 45 analysed): 10 mg IV four times a day.

EBM comments:

1. *Do the methods allow the accurate testing of the hypothesis?*
Yes. However the effects of combined therapy must be

The evidence (EN = enteral nutrition):

Outcome	Time to outcome	Erythromycin ER	Metoclopramide ER	RRR	ARR	NNT
Successful EN at 24 hours	24 hours	87%	62%	29%	25%	4
		95% confidence intervals:		9 to 49%	7.7 to 42.3%	2 to 13
Successful EN at 72 hours	3 days	47%	27%	43%	20%	5
		95% confidence intervals:		1 to 84%	5 to 39.5%	3 to 207
Successful EN at day 7	7 days	31%	16%	48%	15%	NS
		95% confidence intervals:		ns	ns	ns

Rescue therapy (51 patients)	
Duration	Successful EN rate
24 hours	92%
3 days	89%
6 days	67%

- interpreted with care as this phase of the study was non-blinded, uncontrolled and under-powered.
2. *Do the statistical tests correctly test the results to allow differentiation of statistically significant result?* **Yes.** Powered to detect a 20% difference in the rate of successful feeding. Tests seem appropriate. They describe the two groups as “similar” in demographics including diagnosis, but there are statistically significant differences (using chi squared) with more sepsis and less trauma in the erythromycin group. These were not among the factors associated with poor response to prokinetics.
 3. *Are conclusions valid in light of the results?* **Partly** – erythromycin is more effective than metoclopramide in treating feed intolerance as they have defined it. However the effectiveness of both diminishes over time. Although combination therapy may provide a more sustained improvement it will need further investigation with an adequately powered, randomised controlled trial.
 4. *Did results get omitted, and why?* **Yes.** (see study patients)
 5. *Did they suggest areas of further research?* **Yes.** Further investigation of combination therapy and potential role as first line, role of prokinetics such as tegaserod (5HT₄ partial agonist) and loxiglumide (CCK- A antagonist).
 6. *Did they make recommendations based on the results and were they appropriate?* “the short term use of low-dose erythromycin is a reasonable approach for the treatment of feed intolerance in critical illness”. Probably appropriate – difficult to say without more evidence on antibiotic resistance and adverse effects.
 7. *Is this study relevant to my clinical practice?* **Yes** – feed intolerance is a common problem. This trial uses the surrogate marker of residual gastric volume to measure the success of enteral feeding. There are no measures of clinical outcomes such as mortality, length of stay, nutritional state or ventilator associated pneumonia (related to gastric paresis and aspiration). Other studies of prokinetics and post-pyloric feeding have failed to show outcome benefit despite reduced gastric volumes.
 8. *What level of evidence does this study represent?* **1+**
 9. *What grade of recommendation can I make on this result alone?* **B**
 10. *What grade of recommendation can I make when this study is considered along with other available evidence?* **A** (for improving gastric motility – no studies on prokinetics have shown clinical outcome benefit)
 11. *Should I change my practice because of these results?* **Possibly.** Erythromycin seems a better single agent prior to combination therapy for non-responders. Future, larger studies ruling out antibiotic resistance as a concern would be reassuring. Prolonged single agent use seems ineffective.
 12. *Should I audit my current practice because of these results?* **Yes.**

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