Erythromycin for Gastric Emptying in Patients undergoing General Anesthesia for Emergency Surgery.

A Randomized Clinical Trial

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ABSTRACT

IMPORTANCE Patients undergoing emergency procedures under general anesthesia have impaired gastric emptying and are at high risk of aspiration of gastric contents.

OBJECTIVE To evaluate the efficacy of erythromycin, which has strong gastric prokinetic properties, to clear the stomach in emergency patients.

DESIGN, SETTING, AND PARTICIPANTS The ERYTHRO-EMERGE trial was a single center, randomized, double-blinded, placebo-controlled trial in patients undergoing emergency surgery under general anesthesia. 132 patients were included between March 2009 and April 2013 and all completed the study. Randomization was stratified for trauma and non-trauma procedures.

INTERVENTIONS Patients were randomized to either intravenous erythromycin 3 mg kg^{-1} or placebo 15 minutes prior to tracheal intubation. Patients were followed-up for 24 hours.

MAIN OUTCOMES AND MEASURES The primary outcome was clear stomach, defined as <40 ml liquids and no solids, identified through endoscopy immediately after intubation. The secondary outcome was pH of residual gastric content.

RESULTS Clear stomach was diagnosed in 42 of 66 (63.6%) patients receiving placebo as compared with 53 of 66 (80.3%) patients receiving erythromycin (risk ratio [RR], 1.26 [95%CI 1.01-1.57]). In non-trauma patients, the association between erythromycin and clear stomach was statistically significant (adjusted odds ratio [OR] 13.4; 95%CI 1.49-120); in trauma patients, it was not (adjusted OR 1.81; 95%CI 0.64-5.16). Median pH of residual gastric liquid was 2 (interquartile range [IQR] 1-4) in 36 patients receiving placebo, and was 6 (IQR 3-7) in 16 receiving erythromycin (P=0.002). Patients receiving erythromycin had more often nausea (30% versus 6.1%) and stomach cramps (22.7% versus 3.0%). One patient receiving erythromycin vomited before induction.

CONCLUSIONS AND RELEVANCE In patients undergoing general anesthesia for emergency procedures erythromycin increased the proportion of clear stomach and decreased acidity of residual gastric liquid. Erythromycin was particularly efficacious in non-trauma patients. Adverse effects were minor. Further large-scale studies are warranted to confirm the potential of erythromycin to reduce the incidence of broncho-aspiration in emergency patients.

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In the US, about 40 million patients undergo a general anesthetic each year,[1] and approximately 12,000 broncho-aspirate.[2] Broncho-aspiration of gastric juice may lead to acute respiratory distress syndrome,[3] carrying a 40% mortality rate.[4] The risk is increased 10-fold in patients undergoing emergency surgery.[5] Trauma patients may have ingested food before their accident, or have swallowed blood from oral or nasal injuries. Also, gastric emptying is delayed due to head injury, stress, pain, and opioid medication.[6-9] Non-trauma patients may have delayed gastric emptying due to paralytic ileus, critical illness, or cytokine release, leading to significant residual stomach content even after long fasting periods.[10,11]

Strategies have been proposed to decrease the risk of broncho-aspiration. The efficacy and safety of digital pressure on the cricoid cartilage to occlude the upper esophagus during tracheal intubation,[12] have been challenged.[13] As non-acid gastric liquid is considered less deleterious,[14,15] pre-medication with antacids, H2-receptor antagonists, or proton pump inhibitors have been advocated.[15,16] Another approach would be to facilitate gastric emptying or drainage. Clearly, a patient with an entirely empty stomach cannot regurgitate and broncho-aspirate. Stomach drainage with a gastric tube[17] does not guarantee complete emptying. Also, preoperative insertion of a gastric tube in a non-sedated patient is not without hazards,[18] and is only recommended in patients with bowel obstruction. An alternative would be to administer a pro-kinetic drug before induction of anesthesia.[19] Erythromycin, a macrolide antibiotic, and motilin receptor agonist induces antral contractions,[20-22] and increases the lower esophageal sphincter tone,[23-26] which is an important barrier against gastro-esophageal reflux.[27] Although gastric emptying properties of erythromycin have been confirmed in various settings,[28-36] its efficacy in patients undergoing emergency surgery has never been investigated.

We aimed to investigate whether erythromycin clears the stomach of patients undergoing general anesthesia for emergency surgery.

METHODS

Study design

This study was a single center, randomized, placebo-controlled, double-blinded trial, stratified into trauma related surgery and surgery for medical reasons - for instance, acute abdomen. The protocol was approved by the Institutional Ethics Committee (protocol N° NAC 06-225) and the Swiss agency for therapeutic products (SWISSMEDIC, 2008 DR 2321), was inspected by SWISSMEDIC, and monitored by the Clinical Trials Centre of Geneva University Hospitals. Written informed consent was obtained from all patients.

Patients

Adult patients, requiring general anesthesia for emergency surgery were eligibile. Exclusion criteria were American Society of Anesthesiology status > III; allergy to erythromycin; concomitant use of drugs interfering with erythromycin metabolism (for instance, terfenadine); intermittent porphyria; severe liver or renal disease; severe asthma, exacerbated chronic obstructive lung disease, or acute pulmonary infection; acute coronary heart disease, decompensated cardiac insufficiency, or aortic aneurysm; esophageal and pharyngeal disease; status after gastric surgery; need for an immediate surgical intervention; Glasgow Coma Scale <13; inability to understand the study protocol; obstructive ileus; gastric tube; and pregnant or breast feeding women.

Randomization and masking

Hospital pharmacy performed randomization (ratio 1:1) and prepared study medications in numbered 10 ml syringes of erythromycin 3% and matching placebo (physiological saline). The content of a syringe was added to 90 ml physiological saline. Of this solution, 1 ml per kg bodyweight was administered intravenously over five minutes (corresponding to 3 mg kg^{-1} of erythromycin).[36] Allocation sequence was concealed until study end.

Procedures

Unpremedicated patients were randomized to the study drugs upon arrival in the operating room. Fifteen minutes after drug administration, patients were pre-oxygenated during three minutes. General anesthesia was induced with a classic rapid sequence procedure,[37,38] and maintained at the discretion of the attending anesthetist. Immediately after intubation, one of three senior gastroenterologists (JLF, LS, EG) performed an endoscopy (Endoscope GIF, Olympus, Hamburg, Germany) for qualitative and quantitative assessment of gastric content. The working channel of the endoscope (inner diameter, 9 mm) was used to aspirate gastric liquid. The volume of the aspirate was quantified using a ml-graded recipient and when gastric content could not be aspirated (solid food, mixture of liquid and food), it was visually estimated (the opened forceps of the endoscope measures 7 mm in diameter; the volume of solid food was estimated as a multiple of this diameter).

Outcomes

As there was no consistent definition of what should be considered clear stomach in surgical patients,[39] we defined clear stomach as a residual volume of <40 ml and absence of solid food. We performed a sensitivity analysis using "no liquid and no solid" as an alternative, more stringent, definition of clear stomach. The secondary endpoint was the acidity (pH indicator strips 0-14, Merck, Darmstadt, Germany) of residual stomach contents. Additional endpoints were volume and composition of residual gastric content (liquid only, solid only, mixture of liquid and solid), delay between last oral intake and time of endoscopy, and preoperative opioid and antacid medication. In trauma patients, an Injury Severity Score was computed.[40] In non-trauma patients, the diagnosis was recorded. As emergency patients are likely to have stress-induced hyperglycemia, which may reduce erythromycin-induced acceleration of gastric emptying,[41] blood glucose was measured (Contour blood glucose meter, Bayer, Zürich, Switzerland).

Safety endpoints included pre-induction arrhythmia,[42] stomach cramps, and nausea or vomiting. Patients were visited 24 hours after study drug administration and monitored for any adverse effects that could have occurred in relation with the study.

Sample size

Based on a trial that evaluated the efficacy of erythromycin in patients with gastrointestinal bleeding, [36] we assumed a baseline incidence of 30% clear stomach with placebo, and expected that erythromycin would increase this proportion to 80% (absolute risk difference, 50%). A sample of 20 patients per group was required (90% power, two-sided test, type I error of 0.05). To allow for dropouts, and enable subgroup analyses (trauma *versus* non-trauma), we intended to randomize 100 patients (25 patients for each stratum).

After randomization of 100 patients, an estimation of the baseline incidence of clear stomach in our study population (without opening the randomization code) showed that 76% of patients had clear stomach. Therefore, if erythromycin was 100% efficacious, the incidence of clear stomach with placebo could not have been lower than 52% (76-50=26; 26/50=0.52), which was higher than we expected.[36] Additionally, seeking an absolute increase of 50% in the incidence of clear stomach with erythromycin had become illusory. Consequently, we revised the initial power calculation assuming a baseline incidence of clear stomach of 50% but maintaining the aim of increasing that incidence to 80% with erythromycin. We randomized an additional 32 patients (16 patients per group) to reach 90% power to detect this smaller absolute risk difference (two-sided test, type I error 0.05). The protocol was amended accordingly and approved by the institutional Ethics Committee and SWISSMEDIC.

Statistical methods

The crude association between exposure to study treatment and primary endpoint was analyzed and reported using odds ratios (OR) or risk ratios (RR) with 95% confidence intervals (CI). Crude associations between all potential confounding variables and the primary endpoint in the placebo group were analyzed separately. Each variable that was associated with the primary endpoint in the placebo group was entered into a bivariate logistic regression model including study treatment and primary endpoint. Crude and adjusted estimates were compared to assess the degree of potential confounding. When the crude and adjusted estimates differed by more than 10%, the variable was

included into a final multivariable model including all potential confounders. The impact of each variable on the fit of the model was tested using a likelihood ratio test. If the P-value of the test was <0.1, the potential confounder was kept in the model, otherwise it was excluded. Interaction between populations (trauma *versus* non-trauma) and study treatment was tested by introducing an interaction term into the model; if the fit of the model to the data was increased by the interaction term, the results were presented separately for the two strata. Sensitivity analyses using the alternative definition of clear stomach were performed similarly. Continuous secondary endpoints were compared using non-parametric test of equality of distributions. Adverse effects were compared using univariate analysis and reported as OR with 95% CI. Analyses were performed with STATA (Release 11; StataCorp LP, College Station, Texas).

RESULTS

Patients

Between March 25, 2009, and April 10, 2013 we randomized 66 trauma and 66 non-trauma patients to receive erythromycin or placebo (figure 1). All patients received the assigned study treatment, and all had endoscopy performed and the primary endpoint evaluated. All analyses are intention to-treat. The two groups were balanced regarding baseline characteristics (table 1).

Outcomes

Clear stomach, defined as <40 ml liquid and no solid, was diagnosed in 42 of 66 (63.6%) patients receiving placebo and in 53 of 66 (80.3%) receiving erythromycin (RR 1.26; 95%CI 1.01-1.57) (figure 2).

Clear stomach, defined as no liquid and no solid, was diagnosed in 24 of 66 (36.4%) patients receiving placebo and in 40 of 66 (60.6%) receiving erythromycin (RR 1.67; 95%CI 1.15-2.42) (figure 2).

Multivariable analyses

Variables associated with the primary endpoint in the placebo group were study population (trauma vs non-trauma), age, body weight, blood glucose, delay since last oral intake, and preoperative opiate use (table 2). In a bivariate logistic regression model, body weight and delay between last intake and endoscopy changed the crude OR point estimate by more than 10%. When these variables were included into the multivariate model, the association between erythromycin and clear stomach increased (adjusted OR 2.96; 95%CI 1.28-6.83). Introducing an interaction term between population (trauma *versus* non-trauma) and study treatment significantly increased the fit of the model to the data; the impact of erythromycin was different according to the population studied.

Subgroup analyses: trauma versus non-trauma patients

In trauma patients, median time since last meal was about 7 hours and since last liquid intake was about 9 hours (appendix A). 83.3% had received opiates, and 7.6% antacids. The median Injury Severity Score was 4 (IQR 4-9). Of 41 trauma patients with residual gastric content, 21 (51.2%) had liquid only and 20 (48.8%) had solid only or a mixture of liquid and solid (appendix B). The association between erythromycin and clear stomach was not statistically significant (adjusted OR 1.81; 95%CI 0.64-5.16) (table 2).

In non-trauma patients, median time since last meal was about 20 hours and since last liquid intake was about 15 hours (appendix A). 21.2% had received opiates, and 47% antacids (appendix A). 85% of non-trauma patients underwent surgery for acute appendicitis or cholecystitis. Of 27 non-trauma patients with residual gastric content, 24 (88.9%) had liquid only and 3 (11.1%) had solid only or a mixture of liquid and solid (appendix B). The association between erythromycin and clear stomach was statistically significant (adjusted OR 13.4; 95%CI 1.49-120) (table 2).

Sensitivity analyses: alternative definition of clear stomach

Using the alternative definition of clear stomach (no liquid and no solid), blood glucose only was associated with the primary endpoint in the placebo group. Including blood glucose into a bivariate logistic regression model did not change the OR point estimate by more than 10% (table 2).

Secondary endpoint

The pH of stomach aspirates could be measured in 52 patients. The median pH was 2 (IQR 1-4) in 36 patients receiving placebo, and was 6 (IQR 3-7) in 16 receiving erythromycin (P=0.002). A pH ≤2 was diagnosed in 20 of 36 (55.6%) patients receiving placebo compared with one of 16 (6.3%) receiving erythromycin (P=0.001). Antacids were administered in 11 of 36 (30.6%) patients receiving placebo in whom gastric pH could be measured, compared with one of 16 (6.3%) receiving erythromycin (P=0.055). In a logistic regression model describing the binary variable pH<2 or >2, and including antacid intake and study treatment, both variables were found to be predictive of pH. The OR for antacid was 5.71 (95%CI 1.19-27.4) for erythromycin was 30.2 (95%CI 3.38-270).

Additional endpoints

The median volume of residual gastric content was 43.5 ml (IQR 15.0-100) in 42 patients receiving placebo, and was 27.5 ml (IQR 10.0-75.0) in 26 patients receiving erythromycin (P=0.380) (appendix B).

Residual volumes tended to be larger in trauma patients (median, 70 ml in 23 patients receiving placebo, 50 ml in 18 patients receiving erythromycin) compared with non-trauma patients (median, 26 ml in 19 patients receiving placebo, 15.5 ml in 8 patients receiving erythromycin) (figure 3, appendix B).

Adverse effects

Stomach cramps and nausea occurred in 20 (30.0%) and 15 (22.7%) patients receiving erythromycin, compared with 4 (6.1%) and 2 (3.0%) patients receiving placebo (P>0.001). One patient in the erythromycin group vomited before induction (Appendix C). There were no episodes of arrhythmia, regurgitation of gastric contents or broncho-aspiration and no major adverse events.

DISCUSSION

This is the first study showing that administration of erythromycin increases the proportion of clear stomach among patients undergoing general anesthesia for emergency surgery. Depending on the definition of clear stomach, the absolute risk reduction ranged from 17% to 24%, equivalent to a number needed to treat of four to six patients to produce one completely cleared stomach. Erythromycin also decreased acidity of stomach liquid. This might be related to erythromycin's inhibitory effect on motilin receptor-mediated acid secretion.[34] Animal data indicate that a gastric pH below 2.4 increases the risk of lung damage.[14,43] Also, when gastric fluid is effectively buffered, higher volumes of aspirates are tolerated.[15,44] We may assume that in surgical patients, erythromycin will decrease the likelihood of significant lung tissue damage should broncho-aspiration occur despite the premedication.

Erythromycin, through its prokinetic properties, more effectively clears stomachs from liquids than solids.[28,29] This may explain why the clearing effect of erythromycin appeared to be particularly strong in non-trauma patients. In these patients, the delay between last oral intake and induction of anesthesia was longer compared with trauma patients since they sometimes waited long periods with nil by mouth until a diagnosis was confirmed and they were finally scheduled for surgery. In emergency patients, liquid may accumulate in the stomach during starving.

Our study has strengths and weaknesses. One strength of our study is randomization, which ensures a balanced distribution of potential known and unknown confounding factors and may explain why we found only 2 variables (body weight, delay between last oral intake and endoscopy) influencing the crude OR by more than 10%. It is possible that future studies may identify yet other factors associated with gastric content and that may act as confounders despite the randomization (for instance, volume of last meal, presence of gastroparesis). Another strength was the use of endoscopy to evaluate gastric content. Estimation of volume of gastric content with aspiration through nasogastric tubes underestimates the volume of residual gastric liquid.[45,46] Also, endoscopy allows for visual inspection of the gastric cavity, and evaluation of solids.

Our study has several weaknesses. Firstly, we did not include patients with mechanical ileus or patients needing immediate emergency surgery. Most non-trauma patients suffered from acute appendicitis or cholecystitis. As appendectomy is the most common emergency general surgical procedure,[47] we may assume that our non-trauma cohort represented daily clinical practice in an emergency center and that our results are likely to be representative of this population. However, trauma patients had a low median Injury Severity Score indicating mostly minor trauma. Secondly, we tested a single erythromycin regimen only. Erythromycin 1.5 mg kg^{-1} enhanced fasting gastric tone, but 3.0 mg kg^{-1}, as in our trial, reduced the duration of meal-induced relaxation.[22,48,49] In a dose finding study, 3.0 mg kg^{-1} was the most effective regimen to enhance gastric emptying in healthy subjects with a reasonable averse effect profile. In surgical patients, no dose finding study has been performed so far. It remains unknown whether higher doses would further increase efficacy or if smaller doses, which may have a better adverse effect profile, are still efficacious. Thirdly, it might be argued that erythromycin should be given earlier. After administration of erythromycin, half times of gastric emptying after a solid meal were reported to be between 40 minutes[29] and 160 minutes.[28] Fourthly, our choice of the primary endpoint may be debated. Clear stomach is a surrogate endpoint as only the prevention of broncho-aspiration is of clinical relevance. There were no episodes of regurgitation or broncho-aspiration. However, our study was not powered to quantify these more severe, but much less frequent, events, and it seems impossible for patients who have no liquid and no solid at all in their stomach to regurgitate, and subsequently aspirate gastric content into their lungs. Fithly, stomach content at the end of surgery remained unknown. Gastric liquid may be secreted during surgery and broncho-aspirated at extubation. However, prokinetic properties of erythromycin persist up to two hours in the fed state.[50,51] Whether pre-treatment with erythromycin decreases the risk of perioperative broncho-aspiration, and thus of pulmonary complications, in non-fasted patients undergoing emergency surgery, remains to be formally shown. Finally, we did not investigate the occurrence of postoperative infection. As with all macrolide antibiotics, induction of bacterial resistance remains a concern. We believe that this concern remained theoretical. We gave a single dose only of erythromycin and the dosage was low compared with a standard antibiotic treatment (1 to 4 g d^{-1}).

We observed stomach cramps and nausea, and one patient vomited during study drug perfusion. It is unlikely that these drug-related adverse effects prevent clinicians from premedicating emergency patients with erythromycin. A longer administration time is likely to reduce these risks as they correlate with plasma concentrations of erythromycin.[52] There were no allergic reactions or episodes of symptomatic cardiac arrhythmia; postoperative electrocardiograms were not performed systematically. These results are in accordance with other single dose erythromycin studies.[33,36,53] In elderly, co-prescription of erythromycin with a statin metabolized through CYP3A4 was shown to increase statin toxicity.[54] It remains unclear, whether these data may be extrapolated to our study. The research agenda includes testing the efficacy of erythromycin in further surgical populations, for instance, children, or women undergoing emergency caesarean section. As erythromycin seemed more effective in producing a clear stomach in non-trauma compared with trauma patients, it would be interesting to perform liquid and solid-phase gastric emptying studies in these populations. This would help to confirm differential effects on solid vs. liquid gastric emptying. Endoscopy should be used to evaluate qualitatively and quantitatively residual stomach content. To confirm the potential of erythromycine to reduce the incidence of broncho-aspiration in emergency patients, a large-scale study is warranted with perioperative regurgitation and broncho-aspiration and its consequences as main outcomes.

CONCLUSIONS

In patients undergoing general anesthesia for emergency procedures, erythromycin increased the proportion of clear stomach and decreased acidity of residual gastric liquid. Erythromycin was particularly efficacious in non-trauma patients. Adverse effects were minor. Further large-scale studies are warranted to confirm the potential of erythromycin to reduce the incidence of broncho-aspiration in emergency patients.

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Drafting of the manuscript: Czarnetzki, Elia, Tramèr.

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REFERENCES

1. American Society of Anesthesiologists. Anesthesia Fast Facts. http://www.asahq.org/For-the-Public-and-Media/Press-Room/Anesthesia-Fast-Facts.aspx. Accessed October 16, 2014.

2. Warner MA, Warner ME, Weber JG. Clinical significance of pulmonary aspiration during the perioperative period. *Anesthesiology.*1993;78(1):56-62.

3. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med.*2001;344(9):665-671.

4. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med.*2005;353(16):1685-1693.

5. Landreau B, Odin I, Nathan N. [Pulmonary aspiration: epidemiology and risk factors]. *Ann Fr Anesth Reanim.*2009;28(3):206-210.

6. Kao CH, ChangLai SP, Chieng PU, Yen TC. Gastric emptying in head-injured patients. *Am J Gastroenterol.*1998;93(7):1108-1112.

7. Stanghellini V, Malagelada JR, Zinsmeister AR, Go VL, Kao PC. Stress-induced gastroduodenal motor disturbances in humans: possible humoral mechanisms. *Gastroenterology.*1983;85(1):83-91.

8. Thompson DG, Richelson E, Malagelada JR. Perturbation of upper gastrointestinal function by cold stress. *Gut.*1983;24(4):277-283.

9. Murphy DB, Sutton JA, Prescott LF, Murphy MB. Opioid-induced delay in gastric emptying: a peripheral mechanism in humans. *Anesthesiology.*1997;87(4):765-770.

10. Nguyen NQ, Ng MP, Chapman M, Fraser RJ, Holloway RH. The impact of admission diagnosis on gastric emptying in critically ill patients. *Crit Care.*2007;11(1):R16

11. Hsu CW, Sun SF, Lee DL, et al. Impact of disease severity on gastric residual volume in critical patients. *World J Gastroenterol.*2011;17(15):2007-2012.

12. Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. *Lancet.*1961;2(7199):404-406.

13. Smith KJ, Dobranowski J, Yip G, Dauphin A, Choi PT. Cricoid pressure displaces the esophagus: an observational study using magnetic resonance imaging. *Anesthesiology.*2003;99(1):60-64.

14. Teabeaut Jr. Aspiration of gastric contents; an experimental study. *Am J Pathol.*1952;28(1):51-67.

15. James CF, Modell JH, Gibbs CP, Kuck EJ, Ruiz BC. Pulmonary aspiration--effects of volume and pH in the rat. *Anesth Analg.*1984;63(7):665-668.

16. Paranjothy S, Griffiths JD, Broughton HK, Gyte GM, Brown HC, Thomas J. Interventions at caesarean section for reducing the risk of aspiration pneumonitis. *Cochrane Database Syst Rev.*2014;2:CD004943

17. Salem MR, Khorasani A, Saatee S, Crystal GJ, El-Orbany M. Gastric Tubes and Airway Management in Patients at Risk of Aspiration: History, Current Concepts, and Proposal of an Algorithm. *Anesth Analg.*2013;118(3):569-579.

18. Kristensen MS, Gellett S, Bach AB, Jensen TK. Hemodynamics and arterial oxygen saturation during preoperative emptying of the stomach. *Acta Anaesthesiol Scand.*1991;35(4):342-344.

19. Kluger MT, Short TG. Aspiration during anaesthesia: a review of 133 cases from the Australian Anaesthetic Incident Monitoring Study (AIMS). *Anaesthesia.*1999;54(1):19-26.

20. Itoh Z, Nakaya M, Suzuki T, Arai H, Wakabayashi K. Erythromycin mimics exogenous motilin in gastrointestinal contractile activity in the dog. *Am J Physiol.*1984;247(6 Pt 1):G688-G694.

21. Peeters T, Matthijs G, Depoortere I, Cachet T, Hoogmartens J, Vantrappen G. Erythromycin is a motilin receptor agonist. *Am J Physiol.*1989;257(3 Pt 1):G470-G474.

22. Bruley des Varannes S, Parys V, Ropert A, Chayvialle JA, Rozé C, Galmiche JP. Erythromycin enhances fasting and postprandial proximal gastric tone in humans. *Gastroenterology.*1995;109(1):32-39.

23. Meissner AJ, Bowes KL, Zwick R, Daniel EE. Effect of motilin on the lower oesophageal sphincter. *Gut.*1976;17(12):925-932.

24. Pennathur A, Cioppi M, Fayad JB, Little AG. Erythromycin, motilin, and the esophagus. *Surgery.*1993;114(2):295-8; discussion 298-9.

25. Chaussade S, Michopoulos S, Sogni P, Guerre J, Couturier D. Motilin agonist erythromycin increases human lower esophageal sphincter pressure by stimulation of cholinergic nerves. *Dig Dis Sci.*1994;39(2):381-384.

26. Chrysos E, Tzovaras G, Epanomeritakis E, et al. Erythromycin enhances oesophageal motility in patients with gastro-oesophageal reflux. *ANZ J Surg.*2001;71(2):98-102.

27. Mittal RK, Balaban DH. The esophagogastric junction. *N Engl J Med.*1997;336(13):924-932.

28. Edelbroek MA, Horowitz M, Wishart JM, Akkermans LM. Effects of erythromycin on gastric emptying, alcohol absorption and small intestinal transit in normal subjects. *J Nucl Med.*1993;34(4):582-588.

29. Mantides A, Xynos E, Chrysos E, Georgopoulos N, Vassilakis JS. The effect of erythromycin in gastric emptying of solids and hypertonic liquids in healthy subjects. *Am J Gastroenterol.*1993;88(2):198-202.

30. Bouvet L, Duflo F, Bleyzac N, et al. Erythromycin promotes gastric emptying during acute pain in volunteers. *Anesth Analg.*2006;102(6):1803-1808.

31. Janssens J, Peeters TL, Vantrappen G, et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. *N Engl J Med.*1990;322(15):1028-1031.

32. 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;28(7):2334-2337.

33. Narchi P, Benhamou D, Elhaddoury M, Locatelli C, Fernandez H. Interactions of pre-operative erythromycin administration with general anaesthesia. *Can J Anaesth.*1993;40(5 Pt 1):444-447.

34. Asai T, Murao K, Shingu K. Pre-operative oral erythromycin reduces residual gastric volume and acidity. *Br J Anaesth.*2000;85(6):861-864.

35. Memis D, Turan A, Karamanlioglu B, et al. Effect of preoperative oral use of erythromycin and nizatidine on gastric pH and volume. *Anaesth Intensive Care.*2002;30(4):428-432.

36. Frossard JL, Spahr L, Queneau PE, et al. Erythromycin intravenous bolus infusion in acute upper gastrointestinal bleeding: a randomized, controlled, double-blind trial. *Gastroenterology.*2002;123(1):17-23.

37. Lysakowski C, Suppan L, Czarnetzki C, Tassonyi E, Tramèr MR. Impact of the intubation model on the efficacy of rocuronium during rapid sequence intubation: systematic review of randomized trials. *Acta Anaesthesiol Scand.*2007;51(7):848-857.

38. Morris J, Cook TM. Rapid sequence induction: a national survey of practice. *Anaesthesia.*2001;56(11):1090-1097.

39. Schreiner MS. Gastric fluid volume: is it really a risk factor for pulmonary aspiration? *Anesth Analg.*1998;87(4):754-756.

40. Lesko MM, Woodford M, White L, O'Brien SJ, Childs C, Lecky FE. Using Abbreviated Injury Scale (AIS) codes to classify Computed Tomography (CT) features in the Marshall System. *BMC Med Res Methodol.*2010;10:72

41. Jones KL, Kong MF, Berry MK, Rayner CK, Adamson U, Horowitz M. The effect of erythromycin on gastric emptying is modified by physiological changes in the blood glucose concentration. *Am J Gastroenterol.*1999;94(8):2074-2079.

42. Tschida SJ, Guay DR, Straka RJ, Hoey LL, Johanning R, Vance-Bryan K. QTc-interval prolongation associated with slow intravenous erythromycin lactobionate infusions in critically ill patients: a prospective evaluation and review of the literature. *Pharmacotherapy.*1996;16(4):663-674.

43. Kennedy TP, Johnson KJ, Kunkel RG, Ward PA, Knight PR, Finch JS. Acute acid aspiration lung injury in the rat: biphasic pathogenesis. *Anesth Analg.*1989;69(1):87-92.

44. Raidoo DM, Rocke DA, Brock-Utne JG, Marszalek A, Engelbrecht HE. Critical volume for pulmonary acid aspiration: reappraisal in a primate model. *Br J Anaesth.*1990;65(2):248-250.

45. Taylor WJ, Champion MC, Barry AW, Hurtig JB. Measuring gastric contents during general anaesthesia: evaluation of blind gastric aspiration. *Can J Anaesth.*1989;36(1):51-54.

46. Søreide E, Søreide JA, Holst-Larsen H, Steen PA. Studies of gastric content: comparison of two methods. *Br J Anaesth.*1993;70(3):360-362.

47. Alder AC, Fomby TB, Woodward WA, Haley RW, Sarosi G, Livingston EH. Association of viral infection and appendicitis. *Arch Surg.*2010;145(1):63-71.

48. Boivin MA, Carey MC, Levy H. Erythromycin accelerates gastric emptying in a dose-response manner in healthy subjects. *Pharmacotherapy.*2003;23(1):5-8.

49. Ritz MA, Chapman MJ, Fraser RJ, et al. Erythromycin dose of 70 mg accelerates gastric emptying as effectively as 200 mg in the critically ill. *Intensive Care Med.*2005;31(7):949-954.

50. Sarna SK, Soergel KH, Koch TR, et al. Gastrointestinal motor effects of erythromycin in humans. *Gastroenterology.*1991;101(6):1488-1496.

51. Annese V, Janssens J, Vantrappen G, et al. Erythromycin accelerates gastric emptying by inducing antral contractions and improved gastroduodenal coordination. *Gastroenterology.*1992;102(3):823-828.

52. Downey KM, Chaput de Saintonge DM. Gastrointestinal side effects after intravenous erythromycin lactobionate. *Br J Clin Pharmacol.*1986;21(3):295-299.

53. Coffin B, Pocard M, Panis Y, et al. Erythromycin improves the quality of EGD in patients with acute upper GI bleeding: a randomized controlled study. *Gastrointest Endosc.*2002;56(2):174-179.

54. Patel AM, Shariff S, Bailey DG, et al. Statin toxicity from macrolide antibiotic coprescription: a population-based cohort study. *Ann Intern Med.*2013;158(12):869-876.

FIGURE LEGENDS

Figure 1. Study Flow of patients in the ErythroEmerge Trial

Figure 2: Risk Ratio for the Primary Outcome.

Figure 3. Volumes of Residual Gastric Contents. Volumes are total volumes of liquids with or without solids. In each subgroup, patients are listed according to decreasing volumes. In the placebo group, non-trauma stratum, patient N° 1 had a residual volume of 900 ml.

	Erythromycin (n=66)	Placebo (n=66)
Age, years	40.5 (31-58)	45.0 (29-55)
Female	22 (33.3%)	21 (31.8%)
Bodyweight, kg	74.5 (65-80)	78.0 (70-85)
Body height, cm	172.5 (164-180)	172.5 (169-180)
Body-mass index	24.3 (22.0-27.7)	25.0 (23.1-27.7)
Time since last solid meal, hr	13.8 (8-20.7)	16.0 (7-24.5)
Time since last liquid intake, hr	8.5 (6.3-16.1)	8.8 (6-18.3)
Pain, visual analogue scale 0-100	40 (10-50)	25 (10-50)
Patients with diabetes	2 (3%)	3 (5%)
Blood glucose, mmol L^{-1}	5.7 (5.1-6.4)	5.8 (5.1-6.5)
Patients receiving opiate preoperatively	34 (51.5%)	35 (53.0%)
Patients receiving antacides preoperatively	16 (24.2%)	20 (30.3%)

Data are median (interquartile range) or number (%). The body-mass index is the weight in kilograms divided by the square of the height in meters. Pain and glycemia were measured at arrival in the operating room.

Table 1: Demographics and baseline characteristics of all randomly assigned patients

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	Clear stomach, definition I (<40 ml liquid, no solid) Placebo group*			Clear stomach, definition I (<40 ml liquid, no solid)			Clear stomach, definition II (no liquid, no solid)		
Variable	Patients no.	OR (95% CI)	P Value	Patients no.	Adjusted OR (95% CI)	P Value	Patients no.	Adjusted OR (95% CI)	P Value
Exposure to study treatment									
Crude OR (erythromycin/placebo)				132	2.33 (1.06-5.12)	0.035	132	2.69 (1.33-5.44)	0.006
Variable associated with clear stomach in placebo group									
Trauma - yes/no	66	0.34 (0.12-0.97)	0.044	132	2.58 (1.12-5.96)	0.027	132	2.84 (1.37-5.86)	0.005
Age - yr	66	0.96 (0.93-1.00)	0.030	132	2.33 (1.05-5.21)	0.038			
Body weight - kg	66	1.04 (1.00-1.08)	0.050	132	2.60 (1.16-5.85)	0.020			
Blood glucose - mmol L^{-1}	66	0.41 (0.23-0.73)	0.003	132	2.31 (1.02-5.27)	0.046	132	2.65 (1.30-5.39)	0.007
Delay since last oral intake - hr	66	1.05 (0.99-1.10)	0.100	132	2.63 (1.17-5.94)	0.019			
Preoperative opiate use - yes/no	66	0.41 (0.14-1.17)	0.097	132	2.43 (1.07-5.50)	0.033			
Adjusted OR (for body weight and delay since last intake)				132	2.96 (1.28-6.83)	0.011			
Trauma				66	1.81 (0.64-5.16)	0.264			
Non-trauma				66	13.4 (1.49-120)	0.021			

*Variables that were shown to be associated with the primary outcome in the placebo group were entered into a bivariate logistic regression model including study treatment and primary outcome. OR=odds ratio; CI=confidence interval.

Table 2: Adjusted outcomes

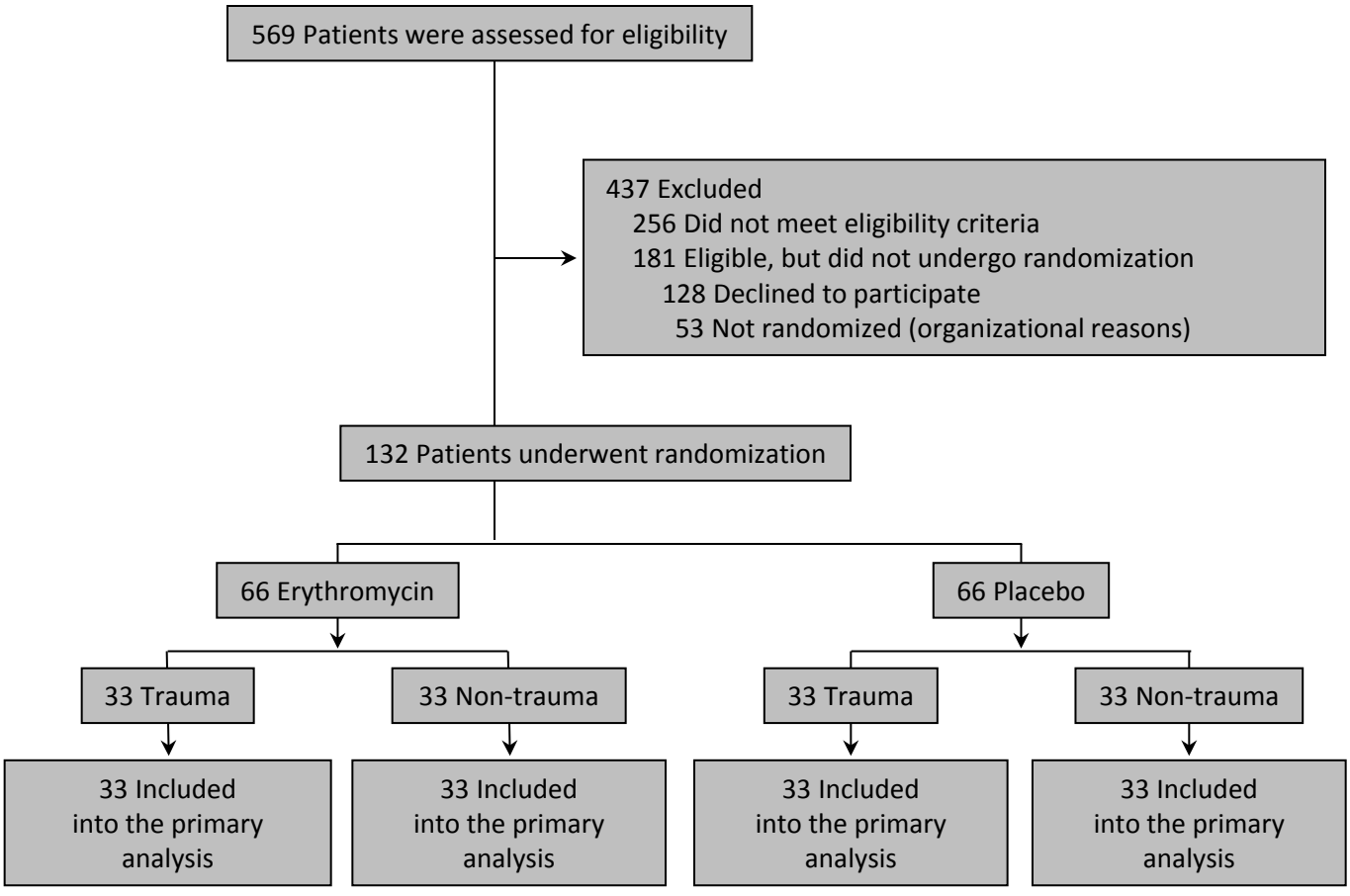

Figure 1. Study Flow of patients in the ErythroEmerge Trial

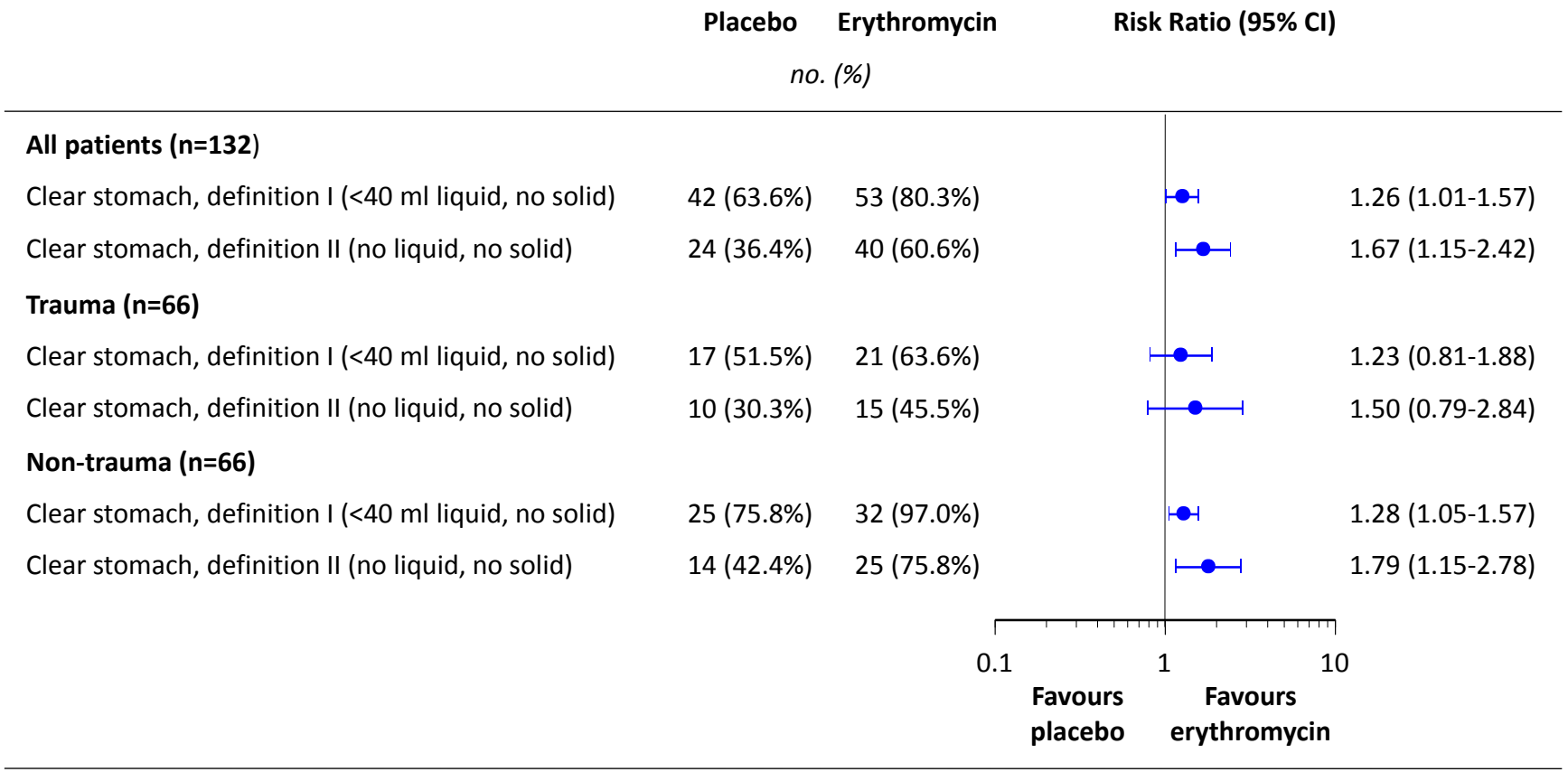

Figure 2: Risk Ratio for the Primary Outcome.

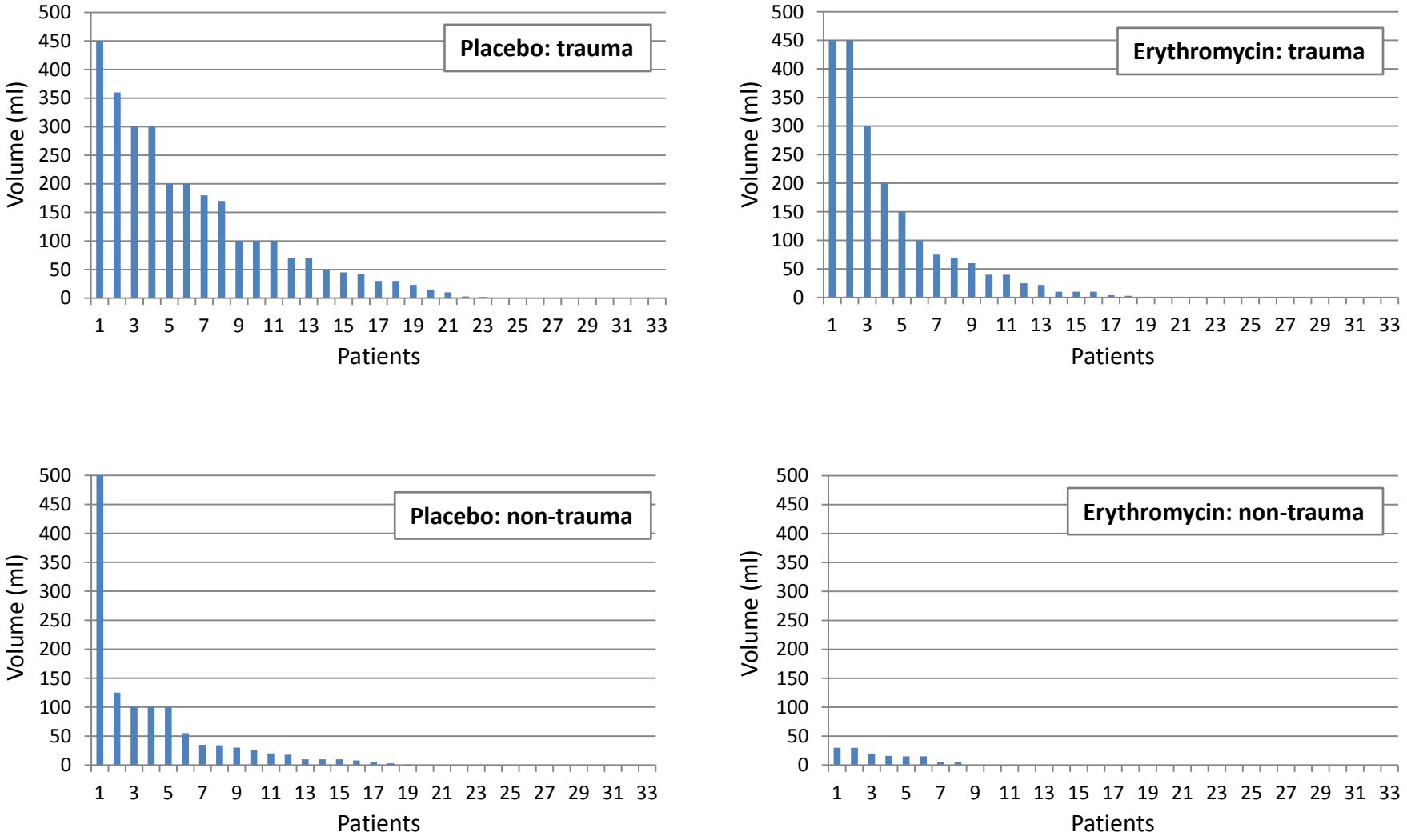

Figure 3. Volumes of Residual Gastric Contents. Volumes are total volumes of liquids with or without solids. In each subgroup, patients are listed according to decreasing volumes. In the placebo group, non-trauma stratum, patient N° 1 had a residual volume of 900 ml.