The Use of Bowel Protocols in Critically Ill Adult Patients: A Systematic Review and Meta-Analysis

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Objective: Constipation is common among critically ill patients and has been associated with adverse patient outcomes. Many ICUs have developed bowel protocols to treat constipation; however, their effect on clinical outcomes remains uncertain. We conducted a systematic review to determine the impact of bowel protocols in critically ill adults.

Data Sources: We searched MEDLINE, Embase, CINAHL, CENTRAL, ISRCTN, ClinicalTrials.gov, and conference abstracts until January 2016.

Study Selection: Two authors independently screened titles and abstracts for randomized controlled trials comparing bowel protocols to control (placebo, no protocol, or usual care) in critically ill adults.

Data Extraction: Two authors independently, and in duplicate, extracted study characteristics, outcomes, assessed risk of bias, and appraised the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation approach.

Data Synthesis: We retrieved 4,520 individual articles, and excluded 4,332 articles during title and abstract screening and 181 articles during full-text screening. Four trials, including 534 patients, were eligible for analysis. The use of a bowel protocol was associated with a trend toward a reduction in constipation (risk ratio, 0.50 [95% CI, 0.25–1.01]; $p = 0.05$; low-quality evidence); no reduction in tolerance of enteral feeds (risk ratio, 0.94 [95% CI, 0.62–1.42]; $p = 0.77$; low-quality evidence), and no change in the duration of mechanical ventilation (mean difference, 0.01 d [95% CI, −2.67 to 2.69 d]; low-quality evidence).

Conclusions: Large, rigorous, randomized control trials are needed to determine whether bowel protocols impact patient-important outcomes in critically ill adults. (*Crit Care Med* 2017; XX:00–00)

Key Words: constipation; critical illness; defecation; gastrointestinal motility; laxatives

Altered gut motility is common among critically ill patients and can manifest as enteral feeding intolerance, diarrhea, or constipation. Risk factors for constipation in the critically ill include the use of opioids or anticholinergic drugs, immobility, and high disease severity (1, 2). Constipation has been associated with adverse outcomes including feeding intolerance (3), delirium (4), increased duration of mechanical ventilation, and hospital stay (3, 5). Multiple observational studies have defined constipation as the failure to pass stool within 72 hours of admission to the ICU; using this definition, the incidence of constipation is as high as 50–83% (1, 3, 6). The European Society of Intensive Care Medicine (ESICM) Working Group on Abdominal Problems adopted this 72-hour cutoff to define "paralysis of the lower gastrointestinal tract" (7); however, in critical care practice, the term "constipation" remains in general use (8).

Standard pharmacotherapies for constipation, including stool softeners and laxatives, have been extensively studied in ambulatory and palliative care settings (9–11). However, bowel care for hospitalized patients, especially those in the ICU, has been a relatively neglected problem (12, 13). Despite a paucity of evidence, it is common for ICUs to develop "in-house" bowel care protocols, using combinations of therapies to treat or prevent constipation (14–16). Although some observational studies have suggested that the use of bowel protocols can decrease the incidence of constipation and diarrhea (1,

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14, 17), others have shown little impact (16). It is also unclear whether the use of bowel protocols can improve downstream patient outcomes. Furthermore, the use of bowel protocols, as opposed to nonprotocolized bowel care, could pose a risk of iatrogenic diarrhea (16), which has its own potential harms, such as electrolyte imbalance, hypovolemia, and recurrent work-ups for infectious diarrhea. Given this equipoise, we performed a systematic review of randomized controlled trials (RCTs) to address the question: "Does the use of a bowel protocol, in comparison to control (placebo, no protocol, or usual care), impact constipation, feeding intolerance, and the duration of mechanical ventilation in critically ill, adult patients?"

MATERIALS AND METHODS

Eligibility

We sought RCTs of any date, published in article or abstract form in any language. Trials had to include adult patients (> 18 yr old), admitted to medical, surgical, or mixed ICUs, with a majority (> 50%) of patients receiving mechanical ventilation. Trials had to compare a bowel protocol (defined as the protocoled use of any of the following: stool softeners, osmotic laxatives, stimulant laxatives, bulking agents, or enemas), to placebo, no protocol, or usual care (which could include ad-hoc, nonprotocoled use of the aforementioned treatments). We excluded trials of patients with primary gastrointestinal disorders (e.g., hepatic encephalopathy, colonic pseudo-obstruction) as these populations may receive elements of the bowel protocol for specific indications (e.g., lactulose for hepatic encephalopathy). We did not judge trial suitability based on reported trial outcomes during the screening stage and excluded otherwise eligible trials from our review only if we were unsuccessful in obtaining unpublished outcome data from trial investigators.

Analytic Framework

We developed an analytic framework based upon narrative reviews (8, 14) and author consensus (**Supplemental Digital Content 1**, http://links.lww.com/CCM/C442). We selected two manifestations of altered gastrointestinal motility (constipation and feeding intolerance) and duration of mechanical ventilation as our primary outcomes. For secondary outcomes, we selected a potential adverse effect of bowel protocols (diarrhea), constipation-associated outcomes (delirium, organ dysfunction), and long-term patient outcomes (length of stay, mortality).

Information Sources and Search Strategy

We conducted a peer-reviewed electronic search of MEDLINE, Embase, CINAHL, and CENTRAL from database inception until January 2016 (**Supplemental Digital Content 2**, http://links.lww.com/CCM/C443). We hand-searched conference abstracts for the American Thoracic Society (2009–2015), Society of Critical Care Medicine (2013–2015), ESICM (2013–2015), and clinical trial databases (ClinicalTrials.gov, ISRCTN). We hand-searched the references of articles undergoing full-text screening for further potentially relevant trials. We obtained additional unpublished information from three trial authors (18–20).

Trial Selection

We exported search results into DistillerSR for eligibility assessment, risk of bias assessment, and data extraction (21). Two reviewers (S.J.W.O., E.H.D.) independently and in duplicate screened titles and abstracts, and assessed full-text articles for eligibility using piloted-tested, standardized forms. We used weighted kappa to assess interrater reliability (22). We arranged for third-party review in the event of primary reviewer disagreement of eligibility, but no disagreements arose.

Data Collection

Each reviewer extracted data using standardized, piloted reporting forms in DistillerSR, using weighted kappa to assess reliability of data extraction (22). Our primary outcomes included 1) incidence of constipation, defined as absence of stools for greater than 72 hours (7); 2) feeding intolerance, as defined by individual trial authors (7); and 3) duration of mechanical ventilation. Our secondary outcomes included 1) incidence of diarrhea, as defined by individual trial authors (7); 2) incidence of delirium, diagnosed with the Diagnostic and Statistical Manual of Mental Disorders (23), Confusion Assessment Method for the ICU (24), or the Intensive Care Delirium Screening Checklist (25); 3) organ dysfunction, measured using the Sequential Organ Failure Assessment (SOFA) score or Multiple Organ Dysfunction Score (26); 4) duration of ICU stay; and 5) hospital mortality.

Risk of Bias in Individual Trials

We assessed risk of bias using the Clinical Advances Through Research and Information Translation (CLARITY) Group's modified Cochrane Database of Systematic Reviews tool, which assesses the domains of random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting (27–29). We judged whether the investigators took sufficient measures to reduce the risk of bias in each domain as "definitely yes," "probably yes," "probably no," and "definitely no" using standardized criteria (28, 29). We arranged for third-party review in the event of primary reviewer disagreement, but no disagreements arose. We calculated weighted kappa to assess interrater reliability of initial judgments of risk of bias (22).

Summary Measures

We entered data from eligible studies into RevMan for analysis (30). We did not assume a common effect size across study populations and therefore chose a random-effects model for our meta-analysis (31). Summarized outcomes (mean difference or standardized mean difference for continuous variables; relative risk for dichotomous variables) and 95% CIs were calculated in RevMan and presented as forest plots. Trial data presented as median and interquartile range were converted to mean and SD (32). For outcomes with insufficient data to permit data pooling, we presented trial results in narrative fashion.

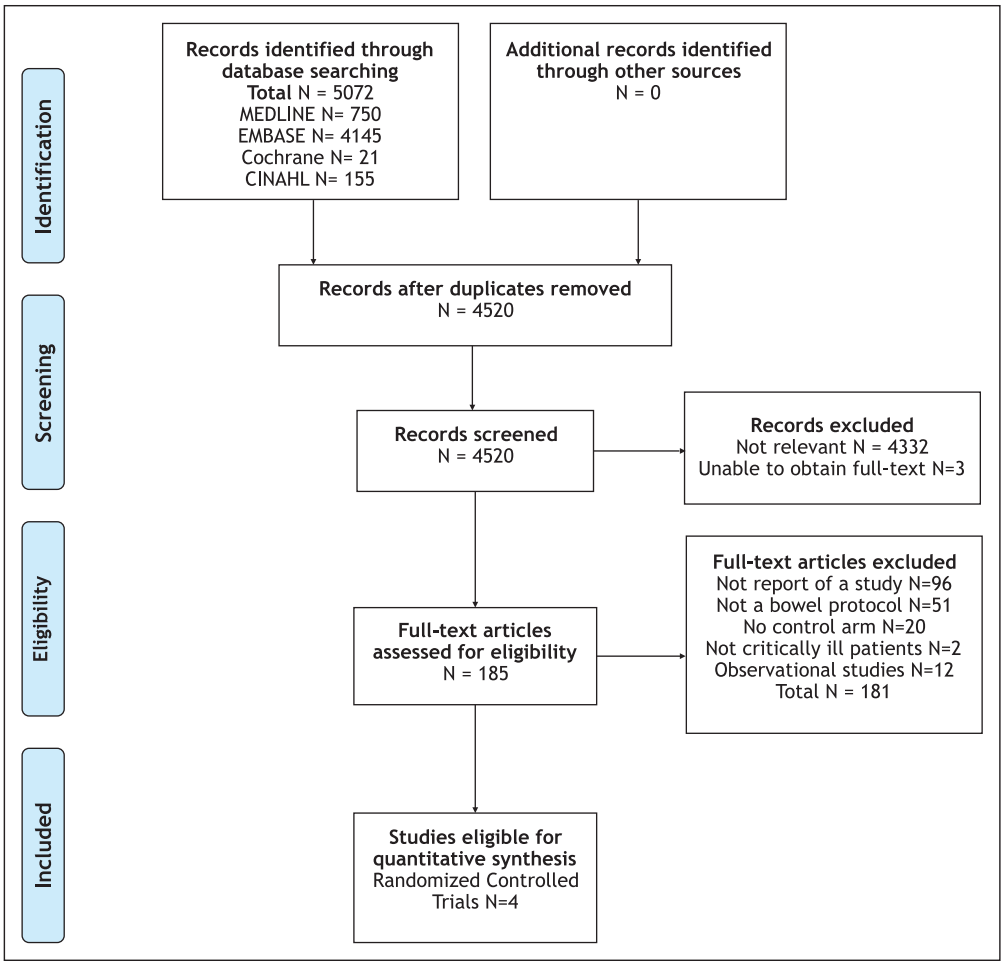

Figure 1. Flowchart showing included and included studies, with reasons for exclusion.

Clinical heterogeneity was assessed by examining the trial populations, interventions, and comparators. Statistical heterogeneity was assessed for each outcome and reported using I^2 calculations and chi-square statistic (with $I^2 > 50\%$ and $p < 0.1$ indicating significant heterogeneity, respectively). We planned subgroup analyses based upon trial characteristics likely to result in heterogeneity (**Supplemental Digital Content 3**, http://links.lww.com/CCM/C444). We planned to assess the risk of bias across trials using inspection of funnel plots if a sufficient number of trials (> 10) were found (27).

Assessment of Quality of Evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate the quality of evidence for each outcome (33). In GRADE, evidence derived from RCTs is initially considered to be of "high" quality but can be rated down after considering the risk of bias across studies; potential biases within each trial (34); and the imprecision (35), inconsistency (36), and indirectness of the evidence (37). We generated GRADE summary of findings' tables using GradePRO software (38–40) and used weighted kappa to assess interrater reliability of GRADE assessments (22).

RESULTS

Initial database searches retrieved 5,072 references, with no additional trials found through conference abstracts or trial databases. After removal of duplicates, 4,520 articles underwent title and abstract screening. We performed full-text screening of 185 articles (weighted κ, 0.72; good agreement), finding four eligible RCTs (weighted κ, 0.86; excellent agreement). We were unable to obtain the full text of three articles, but we considered these unlikely to be eligible. The number of studies identified, and reasons for exclusion are found in **Figure 1**.

Trial Characteristics

The four RCTs were published between 2001 and 2015 (18–20, 41). Two trials were conducted in Europe, one in Asia and one in South America. One trial was conducted in a surgical/trauma ICU, with the remainder in mixed medical/surgical ICUs. All four RCTs randomized patients to a lactulose-based regimen, and one RCT randomized patients to a third arm with a polyethylene glycol (PEG)-based regimen. All trials prohibited the open-label use of bowel care in the intervention arms. In two trials, control groups received matching placebos (18, 19). In one trial, the control group received local ICU bowel protocols (20), and in other trial, the control group was disallowed any bowel care regimen (41). Weighted kappa for risk of bias assessment was 0.42 (fair agreement), with all disagreements resolved by discussion. Study characteristics and risk of bias are listed in **Table 1**. The summary of findings is presented in **Table 2**.

Primary Outcomes

Constipation. Four trials reported on constipation (18–20, 41). Use of a bowel protocol was associated with a nonsignificant trend toward a reduction in constipation (relative risk [RR], 0.50; 95% CI, 0.25–1.01; $p = 0.05$; low-quality evidence). We observed statistical heterogeneity, with an I^2 value of 96%, and chi-square p value of less than 0.01, unexplained by our prespecified subgroup analyses, including ICU type, illness severity, type of laxative or control, timing of bowel protocol, or risk of bias. We rated down the quality of evidence due to imprecision and heterogeneity (**Fig. 2*A***).

Feeding Intolerance. Three trials reported on feeding intolerance, finding no statistically significant reduction with the use of bowel protocols compared with control (RR, 0.94; 95%

TABLE 1. Study Characteristics and Risk of Bias Assessments

Trial	Population	Interventions
de Azevedo et al (20), South America ($n = 88$)	Mechanically ventilated patients < 72 hr, medical and surgical, receiving 20% of calories via enteral nutrition; Age (mean): 51.2; male: 61.4%; APACHE II (median): 19.5; Sequential Organ Failure Assessment (median): 7.5	Lactulose 20 mL enterally every 8 hr, titrated to 1–2 stools/d ($n = 44$); usual care, tolerating absence of defecation for up to 5 d unless obstipation present ($n = 44$)
Masri et al (41), Asia ($n = 100$)	Mechanically ventilated surgical, and trauma patients with expected ICU stay > 72 hr, without contraindications to enteral nutrition. Age (mean): 37.85; male: 79.5%; Simplified Acute Physiology Score 2 (mean): 35	Lactulose 13 g in 20 mL water enterally twice daily for 72 hr, starting within 6 hr of ICU admission followed by usual care ($n = 50$); tolerating absence of defecation for up to 72 hr followed by usual care ($n = 50$)
van der Spoel and Straaten (19), Europe ($n = 308$)	Mechanically ventilated medical, surgical, or cardiovascular patients with multiple organ failure, and no bowel movement in first 72 hr of ICU stay. Age (mean): 66.54; male: 61.7%; APACHE II (mean): 22	Lactulose 13 g in 100 mL water enterally every 8 hr ($n = 110$); Polyethylene glycol 13 g in 100 mL water enterally every 8 hr ($n = 95$); sterile water placebo 100 mL enterally every 8 hr ($n = 103$); all groups received rescue therapy including enema, IV neostigmine, and polyethylene glycol at day 7
Zvoníček et al (18), Europe ($n = 38$)	Mechanically ventilated > 24 hr medical surgical, without pneumonia. Age (mean) 51.2; male: 78.9%; APACHE II (mean): 25	Lactulose 15 mL enterally four times daily ($n = 15$); saline placebo 15 mL enterally four times daily ($n = 23$)

APACHE = Acute Physiology and Chronic Health Evaluation.

This table contains information on the study populations, intervention and control, and assessments of methodologic quality according to the Clinical Advances Through Research and Information Translation (CLARITY) group's risk of bias assessment tool.

CI, 0.62–1.42; $p = 0.77$; low-quality evidence) (18, 20, 41). We rated down the quality of evidence due to imprecision and risk of bias, as the lack of blinding in two trials may have influenced assessments of feeding intolerance (Fig. 2***B***).

Duration of Mechanical Ventilation. Four trials reported on the duration of mechanical ventilation, finding no statistically significant difference with the use of a bowel protocol (mean difference [MD] 0.01 d; 95% CI, –2.67 to 2.69 d; low-quality evidence) (18–20, 41). We rated down the quality of evidence for imprecision, as well as heterogeneity, which was unexplained by our prespecified subgroup hypotheses ($I^2 = 58\%$; χ^2 $p = 0.07$) (Fig. 2***C***).

Secondary Outcomes

Delirium. No trials reported on delirium.

Diarrhea. Only one trial reported on the incidence of diarrhea, finding an increased proportion of days of diarrhea with the use of bowel protocols (median % of days [Q1, Q3], 17.0 [9.3–25.0] vs 6.3 [0–14.7]; $p < 0.001$; low-quality evidence) (20). We rated down the quality of evidence due to imprecision and risk of bias, as the lack of blinding in this trial may have influenced assessments of diarrhea.

Organ Dysfunction. Only one trial reported measures of organ dysfunction, finding a greater reduction in SOFA score with the use of a bowel protocol (median change [Q1, Q3], –4.0 [–6.0 to 0] vs –1 [–4.0 to 1.0]; $p = 0.036$; moderate-quality evidence) (20). We rated down the quality of evidence due to imprecision.

Duration of ICU stay. Four trials reported on ICU length of stay, finding no reduction with the use of a bowel protocol (MD, –0.63 d; 95% CI, –2.1 to 0.85; $p = 0.4$; moderate-quality evidence) (18–20, 41). We rated down the quality of evidence due to imprecision (**Fig. 3*A***).

ICU Mortality. Four trials reported on ICU mortality, finding no reduction in mortality with the use of bowel protocols (RR, 0.90; 95% CI, 0.66–1.23; $p = 0.5$; moderate-quality evidence) (18–20, 41). We rated down the quality of evidence due to imprecision (Fig. 3***B***).

Additional Analyses

We found an insufficient number of trials to permit our subgroup analyses. For the same reason, we did not use a funnel plot to assess for publication bias (27).

DISCUSSION

Our systematic review identified four RCTs evaluating the impact of bowel protocols. We found the quality of evidence was low to moderate. The strengths of this review include the rigorous search strategy: the duplicate conduct of screening, eligibility, data extraction, risk of bias, and evidence appraisal using GRADE, with high interrater reliability. Our review was limited by imprecision due to the small number and size of the relevant trials. Our analysis is likely underpowered and

Risk of Bias Assessment									
Was the Allocation Sequence Adequately Generated?	Was the Allocation Adequately Concealed?	Were Patients Blinded?	Were Healthcare Providers Blinded?	Were Data Collectors Blinded?	Were Outcome Assessors Blinded?	Were Data Analysts Blinded?	Were Missing Outcome Data Infrequent?	Are Reports Free of Suggestion of Selective Outcome Reporting?	Was the Study Free of Other Bias?
Probably yes	Probably no	Definitely no	Definitely no	Definitely no	Probably no	Probably no	Definitely yes	Probably yes	Probably yes
Probably yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Probably yes	Probably no	Definitely yes	Probably yes	Definitely yes
Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Probably no	Definitely yes	Probably yes	Probably yes
Probably yes	Probably yes	Definitely no	Definitely no	Definitely no	Probably no	Probably no	Definitely yes	Definitely yes	Definitely yes

cannot exclude significant harm nor benefit from the use of bowel protocols. Larger, adequately powered trials are needed and should include delirium as an outcome.

Although our broad definition of a "bowel protocol" had the potential to include trials of clinically diverse interventions, all trials we identified used lactulose as the primary laxative. This may be why we observed minimal heterogeneity in many outcomes. The heterogeneity we observed for the outcomes of constipation and duration of mechanical ventilation may be due to cointerventions embedded within the protocols. We were unable to explain this heterogeneity using our prespecified subgroup analyses.

While the consistent use of lactulose within the trials minimized the heterogeneity for many outcomes, it may also limit the generalizability of our findings. It is possible that bowel protocols using other laxatives (e.g., PEG) may have different effects. Indeed, small differences were observed in the two arms of the trial by van der Spoel et al (19). Unfortunately, too few trials exist to permit subgroup analysis of the effectiveness of different laxatives within the bowel protocols. This highlights the scarcity of bowel care research, warranting further RCTs comparing different laxatives in critical care.

Another trial, not included in this review, evaluated neostigmine to induce defecation, finding that among patients who did not have a bowel movement for 72 hours, neostigmine infusion increased the proportion of patients who had a bowel movement (42). We excluded this trial from our review for two reasons. First, as an IV administered agent, we considered neostigmine to be outside the scope of a "bowel protocol." Its role in clinical trials has been as a "rescue agent" in the event that a bowel protocol is unsuccessful (17, 42). Second, the autonomic effects of neostigmine outside the gastrointestinal tract result in a different risk profile from other commonly used agents (43, 44).

Although we did not find any trials of supplemental fiber as a singular component of a bowel protocol, numerous studies evaluating high-fiber versus low-fiber enteral feeds have been published. We decided a priori to exclude such trials, given the wide array of nutritional formulae available, and complex, sometimes varying nutritional requirements of critically ill patients. However, careful use of fiber-containing feeds is another promising management strategy for enhancing gut motility in critical illness, as highlighted in several recent systematic reviews (45–47).

A major challenge in our review was the lack of consistent definitions for gut motility disorders. Standardized outcome definitions (such as the ESICM Working Group definitions) in trials evaluating gut motility disorders would facilitate research in this seemingly neglected area of critical care practice (7). Among the trials we found, diarrhea and feeding intolerance were variably defined, though we recognize that efforts to describe the epidemiology of diarrhea in the ICU are ongoing (48). Most trials used a consistent definition for constipation (> 72 hr without defecation), though prospective observational

TABLE 2. Grading of Recommendations Assessment, Development, and Evaluation Summary of Findings Table

Outcome		Anticipated Absolute Effects (95% CI)			
No. of Participants (Trials)	Relative Effect (95% CI)	Without Bowel Protocol	With Bowel Protocol	Difference	Quality
Constipation No. of participants: 534 (four trials)	Relative risk 0.50 (0.25–1.01)	Study population 77.7% Moderate 72.7%	38.9% (19.4–78.5) 36.4% (18.2–73.5)	38.9% fewer events (58.3 fewer to 0.8 more) 36.4% fewer events (54.5 fewer to 0.7 more)	⊕⊕○○ Low[a,b]
Feeding intolerance No. of participants: 226 (three trials)	Relative risk 0.94 (0.62–1.42)	Study population 25.6% Moderate 43.2%	24.1% (15.9–36.4) 40.6% (26.8–61.3)	1.5% fewer events (9.7 fewer to 10.8 more) 2.6% fewer events (16.4 fewer to 18.1 more)	⊕⊕○○ Low[c,d]
Duration of mechanical ventilation No. of participants: 226 (three trials)	–	The mean duration of mechanical ventilation was 13.1 d	–	Mean difference 0.01 d higher (2.67 lower to 2.69 higher)	⊕⊕○○ Low[e,f]
Diarrhea No. of participants: 88 (one trial)	–	The median proportion of days with diarrhea was 7.0 d	–	Mean difference 10.1 d higher (5.23 higher to 14.97 higher)	⊕⊕○○ Low[a,g]
Organ dysfunction No. of participants: 88 (one trial)	–	The mean organ dysfunction score was 5.5 U	–	Mean difference 1.5 U lower (3.02 lower to 0.02 higher)	⊕⊕⊕○ Moderate[g]
Length of ICU stay No. of participants: 534 (four trials)	–	The mean length of ICU stay was 13.25 d	–	Mean difference 0.63 d fewer (2.1 fewer to 0.85 more)	⊕⊕⊕○ Moderate[h]
ICU mortality No. of participants: 534 (four trials)	Relative risk 0.90 (0.66–1.23)	Study population 23.2% Moderate 28.5%	20.9% (15.3 to 28.5) 25.7% (18.8 to 35.1)	2.3% fewer deaths (7.9 fewer to 5.3 more) 2.9% fewer deaths (9.7 fewer to 6.6 more)	⊕⊕⊕○ Moderate[i]

[a]Absence of blinding in two studies for potentially subjective outcomes, inclusion of these unblinded studies affects the overall estimate of effect.

[b]Significant heterogeneity ($I^2 = 97\%$); likely due to differences in underlying study populations (Masri et al [41] is a predominantly surgical population, cf. the other two studies which were predominantly medical populations).

[c]Optimal information size (OIS) not met, OIS ~ 1,300 events for relative risk (RR) of 25% with event rate of 25%.

[d]Episodes of feeding intolerance in Zvoníček et al (18) calculated using reported mean episodes of feeding intolerance, reducing precision.

[e]Significant heterogeneity ($I^2 = 58\%$) unexplained by a priori hypotheses.

[f]OIS not met, OIS > 1,000 for mean difference (MD) 0.01 d.

[g]Only reported in one trial.

[h]95% CI of estimated MD fails to exclude significant benefit or harm.

[i]OIS not met, OIS > 2,000 events for RR of 10% with event rate of 25%.

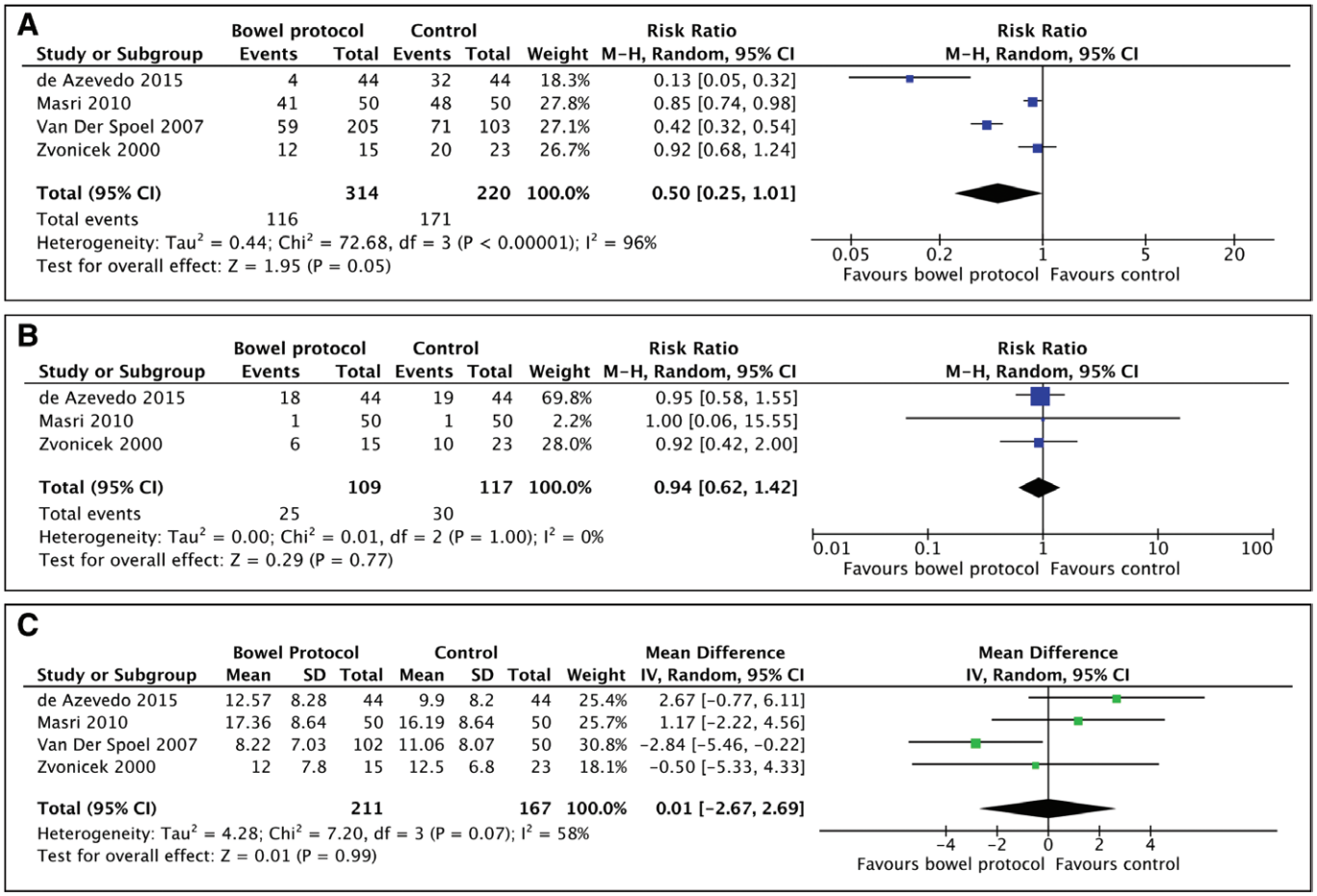

Figure 2. Forest plots for primary outcomes. **A**, Constipation. **B**, Feeding intolerance. **C**, Duration of mechanical ventilation, in days.

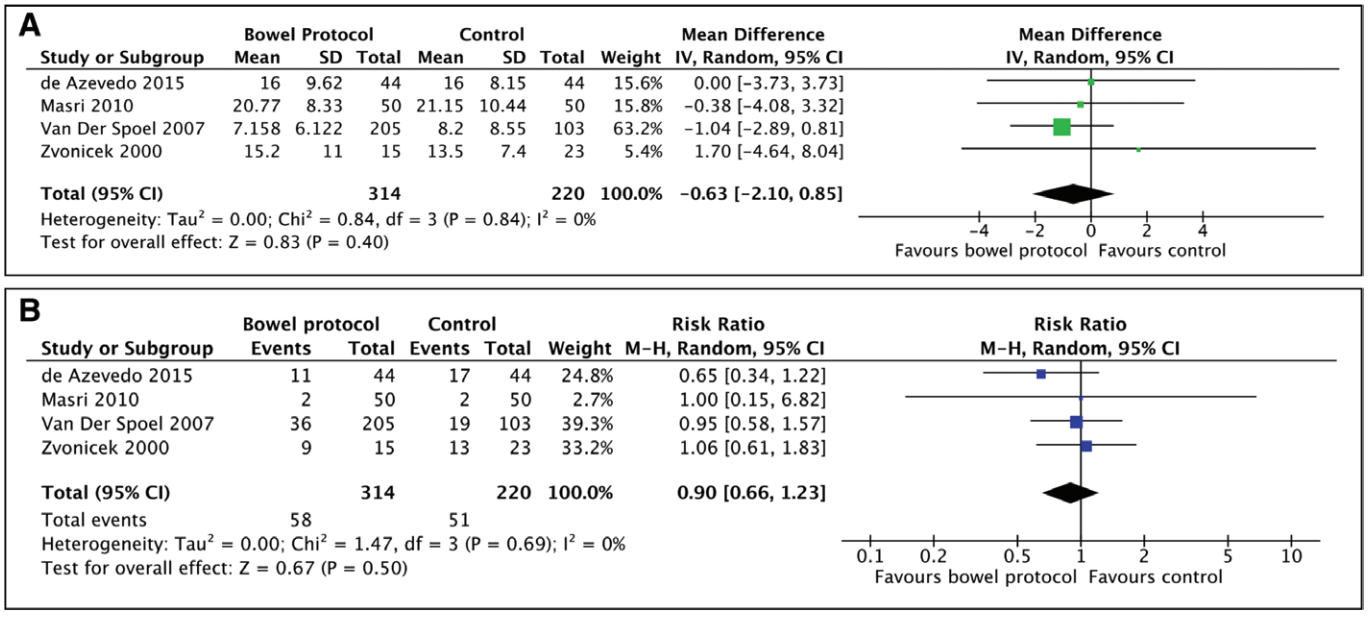

Figure 3. Forest plots for secondary outcomes. **A**, Duration of ICU stay, in days. **B**, ICU mortality.

data and post hoc analyses in the trial by van der Spoel et al (19) suggest that a definition of "6 days without defecation" may better predict adverse outcomes (e.g., increased duration of mechanical ventilation and ICU stay), in critically ill patients. This definition may identify patients in whom bowel protocols have a greater impact, and warrants further study (49).

Finally, our review was limited to common patient-level outcomes. Bowel protocols may have important effects on other outcomes, such as clinician convenience; standardization of care, reduced testing for *Clostridium difficile* infection, and avoidance of rare events effects such as stercoral colitis (14, 16, 50). This highlights the importance for a collaborative approach, including multiple stakeholders—nurses, dieticians, pharmacists, and physicians—to providing bowel care in the ICU.

CONCLUSIONS

We found low-to-moderate–quality evidence comparing the use of bowel protocols to control (placebo, no protocol, or usual care). There is insufficient evidence to deduce that bowel protocols improve constipation, feeding intolerance, or duration of mechanical ventilation. These results are limited by imprecision due to the small number and sample size of trials. Given the ubiquity of bowel protocols in many ICUs, large, rigorous trials are needed to determine whether bowel protocols improve clinical outcomes in critically ill adults.

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