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Diarrhea during critical illness: a multicenter cohort study

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Abstract

Purpose: To study the incidence, predictors, and outcomes of diarrhea during the stay in the intensive care unit (ICU).

Methods: Prospective cohort of consecutive adults in the ICU for > 24 h during a 10-week period across 12 intensive care units (ICUs) internationally. The explored outcomes were: (1) incidence of diarrhea, (2) *Clostridioides difficile*-associated diarrhea (CDAD); (3) ICU and hospital length of stay (LOS) and mortality in patients with diarrhea. We fit generalized linear models to evaluate the predictors, management, morbidity and mortality associated with diarrhea.

Results: Among 1109 patients aged 61.4 (17.5) [mean (standard deviation)] years, 981(88.5%) were medical and 645 (58.2%) were mechanically ventilated. The incidence was 73.8% (818 patients, 73.8%, 95% confidence interval [CI] 71.1–76.6) using the definition of the World Health Organisation (WHO). Incidence varied across definitions (Bristol 53.5%, 95% CI 50.4–56.7; Bliss 37.7%, 95% CI 34.9–40.4). Of 99 patients with diarrhea undergoing CDAD testing, 23 tested positive (2.2% incidence, 95% CI 1.5–3.4). Independent predictors included enteral nutrition (RR 1.23, 95% CI 1.16–1.31, $p < 0.001$), antibiotic days (RR 1.02, 95% CI 1.02–1.03, $p < 0.001$), and suppositories (RR 1.14 95% CI 1.06–1.22, $p < 0.001$). Opiates decreased diarrhea risk (RR 0.76, 95% CI 0.68–0.86, $p < 0.001$). Diarrhea prompted management modifications (altered enteral nutrition or medications: RR 10.25, 95% CI 5.14–20.45, $p < 0.001$) or other consequences (fecal management device or CDAD testing: RR 6.16, 95% CI 3.4–11.17, $p < 0.001$). Diarrhea was associated with a longer time to discharge for ICU or hospital stay, but was not associated with hospital mortality.

Conclusion: Diarrhea is common, has several predictors, and prompts changes in patient care, is associated with longer time to discharge but not mortality.

Keywords: Diarrhea, Enteral nutrition, Incidence, Predictors, Critical illness

Introduction

The reported incidence of diarrhea during critical illness ranges from 2 to 95% [1, 2]. Differentiating diarrhea from changes in stool frequency, consistency, and volume that commonly occur during admission to the intensive care unit (ICU) is challenging [3]. Moreover, wide variation exists regarding what is considered a normal bowel habit in the general population [4], with definitions ranging from 3 bowel movements per week to 2–3 per day. Thus, there is no universal definition for what constitutes diarrhea in the ICU [5].

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The World Health Organization (WHO) definition of diarrhea is the passage of 3 or more liquid stools per day [6], as adopted by the European Society of Intensive Care Medicine Abdominal Problem Working Group [3]. Perhaps the most recognized stool evaluation instrument in hospitals is the Bristol Stool Chart [7], which is simple and easily applied at the bedside, composed of descriptive text and a figure depicting each of the seven categories. The Bristol Stool Chart better predicts whole-intestinal transit time than stool frequency [7], and is used to define diarrhea associated with *Clostridioides difficile* by the European Society for Clinical Microbiology and Infectious Disease [8, 9]. The Bliss Stool Classification System has 4 categories with depictions and descriptions for each category. Despite reliability and validity when utilized by health care professionals [10, 11], this instrument is not widely used in research. Investigations in the ICU setting have employed the Bristol Stool Chart [12]; however, large studies validating these classification systems in critical illness are lacking.

Epidemiology of diarrhea in critically ill patients is limited in quality and quantity. A recent systematic review identified 8 observational studies of diarrhea in this setting [5]. Studies have reported on diarrhea in enterally fed critically ill patients [13], diarrhea predictors [14, 15] and manifestations of gastrointestinal failure (e.g., feeding intolerance and ileus) [16]. Designs included retrospective audits, registry analyses [14], case–control [16] and single-center studies[17]. Another recent systematic review included 12 prospective studies of diarrhea in the ICU [18]; from the final sample of 12,624 patients, the 1888 patients with diarrhea compared to those without had an associated increased ICU mortality (RR 1.43, 95% CI 1.03, 1.98), an increased length of stay in the ICU (MD 8.08 days, 95% CI 5.85, 10.32) and hospital (MD 9.67 days, 95% CI 2.17 to 17.16) [18].

The objectives of this study were to determine the incidence of diarrhea defined using the WHO criteria, including the incidence of *Clostridioides difficile*-associated diarrhea (CDAD), to compare the incidence and definitions of diarrhea using the Bristol Stool Chart and Bliss Classification System, to identify diarrhea predictors, and to describe the management modifications, consequences, and clinical outcomes associated with diarrhea.

Take-home message

In this study, we demonstrated that diarrhea was common in the intensive care unit, and rarely was *Clostridioides difficile* the cause. Diarrhea incidence varied based on the definition applied. Diarrhea was associated with longer time to discharge but not increased mortality.

Methods

Study design and population

The "Diarrhea: Interventions, Consequences and Epidemiology in the Intensive Care Unit" (DICE-ICU) Study is a prospective multicenter cohort study enrolling consecutive patients 18 years of age or older admitted to the ICU for ≥ 24 h. Patients were excluded if they were in ICU for < 24 h; second and subsequent admissions were not considered to avoid non-independent observations. The design is reported elsewhere [19], including an internal pilot [20]. Participants were enrolled over a 10-week period in 12 academic and community medical-surgical ICUs in Canada ($n=8$), the United States ($n=2$), Poland ($n=1$), and Saudi Arabia ($n=1$). ICUs were enrolled serially, each determining its own 10-week study period from July 2014–August 2019 (internal pilot 2014–2015, main cohort 2016–2019). Patients were followed daily in the ICU until discharge, then hospital vital status and length of stay was documented, censored at 1 year. DICE-ICU was approved by the research ethics board at each center with a waiver of informed consent except for 1 center which mandated a priori written consent. DICE is reported per STROBE guidelines [21].

Outcomes

The research team trained bedside nurses [19] to track the number and character of each stool daily. The reference standard and primary outcome were the WHO definition of at least 3 liquid bowel movements per day [6]; we also used the Bristol Stool Chart Score of 6 or 7 [7] and Bliss Stool Classification System score of 4 [10] as secondary diarrhea definitions. We used patients' first episode of diarrhea after their admission to ICU as the index case. We defined confirmed CDAD as positive microbiology testing with the presence of diarrhea based on the WHO definition.

Research staff collected baseline patient characteristics (i.e., age, sex, pre-hospital comorbidities, Acute Physiology and Chronic Health Evaluation II (APACHE II) score [22], admission diagnosis and pre-existing gastrointestinal conditions (i.e., inflammatory bowel disease, Celiac disease, short bowel syndrome, prior bowel resection, chronic pancreatitis, and gastroparesis, CDAD, ileostomy or colostomy). Research staff collected daily life support (i.e., invasive mechanical ventilation, vasopressors, renal replacement therapy), laboratory values, enteral nutrition (i.e., formulation, route, volume, and interruptions), medications known to influence the risk of diarrhea, and management modifications and consequence of diarrhea. CDAD testing was performed at the physician's discretion. Mortality and length of ICU and hospital stay were documented, censored at 1 year.

Data were validated by research staff and the principal investigator (JCD) at McMaster University's Methods Center.

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Statistical analysis

The methodology and statistical analysis plan were published [19]. Briefly, our sample size was derived by two approaches: (1) the rule of thumb based on independent predictors and number of events per degree of freedom and (2) the DICE internal pilot primary objectives. Baseline characteristics were analysed descriptively, reported as counts (percent), mean (standard deviation) or median (quartile 1, quartile 3) as appropriate.

The incidence of diarrhea was the proportion of participants who developed diarrhea on day 1 or later in the ICU (WHO as the primary definition), and the Bristol and Bliss scores (secondary definitions). We also calculated the incidence rate (number of new cases of diarrhea divided by person-time at risk in the ICU). The prevalence of CDAD was calculated as the proportion of patients with CDAD upon ICU admission and the number of cases acquired in ICU. The incidence of CDAD was calculated as the proportion of patients with diarrhea subsequently testing positive during their ICU admission (new cases).

Using the kappa statistic, we calculated agreement between the WHO, Bliss and Bristol definitions.

We deviated from the previously published statistical plan [19]. Odds ratios (OR) were the initial estimate of effect planned to be reported in DICE-ICU; however, given the frequency of diarrhea being common rather than uncommon, an RR was determined to be a better estimate of effect (Statistical Appendix).

For all adjusted analyses [23], we used generalized linear models. We specified a log link, a normal distribution (to estimate adjusted risk ratios) with clustered robust standard errors to account for potential clustering within centers. Model comparison was facilitated using Akaike information criteria (AIC). Potential diarrhea predictors (per the WHO definition [6])were determined based on previous studies identifying antibiotics, antifungals, suppository, pro-kinetics, CDAD, and enteral nutrition [2, 13, 14], further refined during the DICE pilot study [20]. The following covariates were entered as a block: baseline factors, such as age (years), sex (female/male), APACHE II score (0–71); exposures in the ICU prior to diarrhea (enteral nutrition (yes/no), and medications [opiates, motility agents, sorbitol, acid suppressants (yes/no), total number of antibiotics (ratio) and the number of days on antibiotics (ratio), and chemotherapy (yes/no)]. We examined the events prior to diarrhea (predictors of diarrhea) separately from the events after diarrhea (consequences of diarrhea). We also analyzed differences in diarrhea predictors for the Bristol Stool Chart and Bliss Stool Classification. We first examined univariate associations. Only predictors that were statistically significant at the $p < 0.05$ threshold were included in the multivariable models.

We fitted similar models to examine the management modifications and consequences of diarrhea adjusting for age, sex, and APACHE II score. Management modifications were any of altered enteral nutrition (i.e., feeds held or decreased, formula changed), stool softener or prokinetic held, or anti-diarrheal agent administered. Management consequences were either fecal management device insertion or CDAD testing. These were all entered as binary (yes/no).

We used the Wilcoxon rank-sum test to compare length of stay in the ICU and hospital between patients with and without diarrhea. To determine the impact of diarrhea on death, ICU discharge and hospital discharge, we attempted to fit Cox proportional hazards models. For the outcome of death at any time, we assumed that discharge was a competing risk, and modelled both failures (death) and competing risk events (discharge). For the outcomes of ICU discharge and hospital discharge, we considered death as a competing risk. In the latter two models, the proportional hazards assumption was not met, so we compared six parametric model distributions (Weibull, Lognormal, Loglogistic, Gompertz, Exponential and Generalized Gamma) and reported the one with the lowest AIC score. All the models were adjusted for age, sex, APACHE score and the standard errors were adjusted for clustering within centres. Hazard ratios (HR), 95% confidence intervals (CI) and p values are reported. Imputation methods were planned a priori in the case of significant missing data [19]. All analyses were performed using Stata (StataCorp, Release 16, 2019, College Station; TX) [24].

Results

From June 2014 to August 2019, 1114 patients were enrolled at 12 academic and community ICUs in Canada, the United States, Poland and Saudi Arabia (Fig. 1), 1109 of whom were included in this study. The mean (standard deviation) age was 61.4 (17.5) years, APACHE II score was 18.8 (8), and 591 (53.2%) were mechanically

ventilated at baseline on study day 1 (Table 1). Most patients were medical (981, 88.5%). Diarrhea-related comorbidities at ICU admission included colectomy or ileostomy (2.4%), and inflammatory bowel disease (0.1%). Our dataset was complete with very few missing data (< 1%), and the imputation was not required. For main outcomes, patients with complete data were used.

Incidence of diarrhea

Based on the WHO definition, 818 of 1109 patients developed diarrhea, for an incidence of 73.8% (95% CI 71.1–76.6); the median (quartile 1–quartile 3) time to diarrhea onset was 2 (1–4) days, for an incidence rate of 224.6/1000 person-days (95% CI 209.5–240.6). The incidence of diarrhea was 53.5% (95% CI 50.4–56.7) using the Bristol Stool Chart and 37.7% (95% CI 34.9–40.4) using the Bliss Stool Classification System. The incidence differed across centers, with a low of 53% and high of 94% (Appendix Table 1).

The prevalence of CDAD (Appendix Fig. 1) in the ICU, including pre-ICU CDAD and ICU-acquired CDAD, was 85/1109 (7.7%, 95% CI 6.2–9.4). A total of 62/1109 (5.5%) had CDAD at admission to ICU. However, among 99 patients tested for CDAD, only 23 were positive (CDAD incidence in the ICU 2.2%, 95% CI 1.5–3.4).

Comparison of the definitions of diarrhea: WHO, Bristol and Bliss

Compared with the WHO definition of diarrhea, agreement with a Bristol Stool Chart score of 6 or 7 was moderate (Kappa = 0.51, 95% CI 0.46–0.55, $p < 0.001$) and with a Bliss score of 4 was fair (Kappa = 0.31, 95% CI 0.27–0.35, $p < 0.001$). The pooled agreement across 3 definitions was fair (Kappa = 0.39, 95% CI 0.36–0.42, $p < 0.001$) (Appendix Fig. 2). The WHO definition of diarrhea identifies more patients with diarrhea and is the definition used for this study.

Predictors of diarrhea

Independent diarrhea predictors (WHO definition) included enteral nutrition (RR 1.23, 95% CI 1.16–1.31, $p < 0.001$), number of antibiotic days (RR 1.02, 95% CI 1.02–1.03, $p < 0.001$) and suppository use (RR 1.14 95% CI 1.06–1.22, $p < 0.001$) (Table 2). Opiates (RR 0.76, 95% CI 0.68–0.86, $p < 0.001$) were associated with decreased diarrhea.

Predictors for diarrhea using the Bristol Stool Chart definition were similar to the WHO definition (Appendix Table 2A, B); however, two additional predictors were age (RR 1.00, 95% CI 1.00–1.01, $p = 0.034$) and total number of antibiotics (RR 1.05, 95% CI 1.01–1.10, $p = 0.019$). Considering the Bliss Stool Classification, diarrhea predictors were similar to the WHO and Bristol definitions, with the addition of female sex (RR 1.11, 95% CI 1.01–1.22, $p = 0.030$) and acid suppressants (RR 1.66, 95% CI 1.15–2.40, $p = 0.007$) (Appendix Table 2A, B).

A post hoc analysis of enteral nutrition composition on the impact of diarrhea in this cohort, after adjustment for antibiotics and suppositories, demonstrated that high osmolarity EN (RR 1.14, 95% CI 1.08–1.20, $p < 0.001$) and high-fiber enteral nutrition (RR 1.11, 95% CI 1.11–1.17, $p < 0.001$) were feeding compositional features associated with diarrhea (Appendix Table 3).

We re-examined age in 5-, 10- and 20-year increments. The differences were too small to see, even when reported to two decimal places. We also analyzed 5-point increments

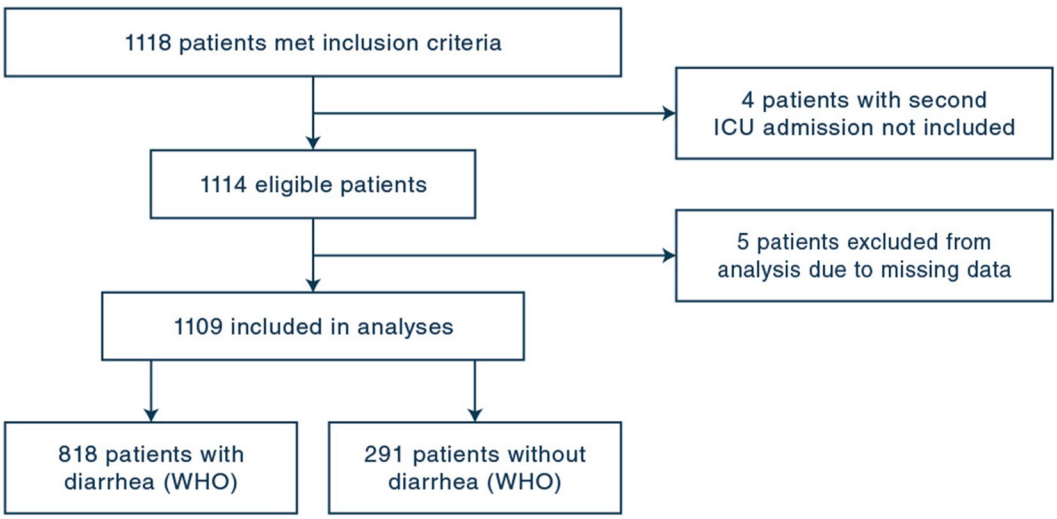

Fig. 1 Flow Diagram for DICE-ICU Study. Flow diagram of patients enrolled in the DICE-ICU Study

Table 1 Baseline Characteristics

Characteristics	Total Cohort (*n* = 1109)	Diarrhea (*n* = 818)	No Diarrhea (*n* = 291)
Sex (female), *n* (%)	489 (44.1)	372 (45.5)	117 (40.2)
Age, mean (SD)	61.4 (17.5)	61.8 (17.2)	60.3 (18.3)
APACHE II score, mean (SD)[a]	18.8 (7.98)	19.1 (7.8)	17.8 (8.5)
Type of patient, *n* (%)[b]			
Medical	981 (88.5)	731 (89.9)	250 (86.5)
Surgical	59 (5.3)	38 (4.7)	21 (7.3)
Trauma	62 (5.6)	44 (5.4)	18 (6.2)
Admitting Diagnosis, *n* (%)[c]			
Cardiovascular	140 (12.6)	95 (11.7)	45 (15.6)
Respiratory	272 (24.5)	214 (26.3)	58 (20.1)
Gastrointestinal	161 (14.5)	119 (14.6)	42 (14.5)
Neurologic	137 (12.4)	98 (12.1)	39 (13.5)
Sepsis	117 (10.6)	95 (11.7)	22 (7.6)
Trauma	62 (5.6)	44 (5.4)	18 (6.2)
Metabolic	86 (7.8)	55 (6.8)	31 (10.7)
Hematologic	10 (0.9)	9 (1.1)	1 (0.3)
Renal	30 (2.7)	24 (3)	6 (2.1)
Gynecologic	2 (0.2)	2 (0.2)	0 (0)
Orthopaedic surgery	14 (1.3)	8 (1)	6 (2.1)
Cardiovascular surgery	6 (0.5)	2 (0.2)	4 (1.4)
Other medical	28 (2.5)	22 (2.7)	6 (2.1)
Other surgical	37 (3.3)	26 (3.2)	11 (3.8)
Location Prior to ICU, *n* (%)[d]			
Emergency room	451 (40.7)	327 (40)	124 (42.6)
Hospital ward	266 (24)	221 (27)	45 (15.5)
OR/Recovery room	221 (19.9)	129 (15.8)	92 (31.6)
Other	46 (4.1)	42 (5.1)	4 (1.4)
ICU (other hospital)	45 (4.1)	38 (4.6)	7 (2.4)
Emergency (other hospital)	58 (5.2)	42 (5.1)	16 (5.5)
Ward (other hospital)	21 (1.9)	18 (2.2)	3 (1)
Relevant comorbid conditions, *n* (%)			
Celiac disease[e]	2 (0.1)	1 (0.1)	1 (0.3)
Irritable bowel	6 (0.5)	5 (0.6)	1 (0.3)
Diabetes	318 (28.7)	229 (28)	89 (30.6)
Prior bowel resection surgery	30 (2.7)	25 (3.1)	5 (1.7)
Inflammatory bowel disease (Crohn disease, ulcerative colitis)	24 (2.2)	22 (2.7)	2 (0.7)
Colectomy/ileostomy	27 (2.4)	21 (2.6)	6 (2.1)
Chronic pancreatitis	10 (0.9)	8 (1)	2 (0.7)
Current *Clostridium Difficile* infection	11 (.1)	9 (1.1)	2 (0.7)
Gastroparesis	7 (0.6)	6 (0.7)	1 (0.3)
Study Day 1, *n* (%)			
Invasive mechanical ventilation[f]	591 (53.2)	455 (55.9)	136 (46.7)
Inotropes or vasopressors[g]	405 (36.5)	304 (37.3)	101 (34.9)
Dialysis/renal replacement[h]	79 (7.1)	59 (7.3)	20 (6.9)

In this table we present baseline characteristics of 1,109 critically ill patients. Surgical patients were defined according to Canadian Critical Care Trials group definition

SD standard deviation, *APACHE* Acute Physiology and Chronic Health Evaluation

[a] 8 missing

[b] 7 missing

[c] 7 missing

[d] 9 missing

Table 1 (continued)

[e] 1 missing

[f] 4 missing

[g] 6 missing

[h] 6 missing

Table 2: Predictors for Diarrhea

Model	Univariate		Multivariable		Multivariable (Reduced)	
Covariates	Crude RR (95% CI)	P-value	Adjusted RR (95%CI)	P -value	Adjusted RR (95%CI)	P-value
Sex (female)	1.00 (1.00–1.00)	0.243	0.94 (0.89–1.00)	0.066		
Age (years)	0.95 (0.86–1.95)	0.276	1.00 (1.00–1.01)	0.101		
APACHE II score (0–71)	1.00 (1.00–1.01)	0.096	1.00 (0.99–1.00)	0.173		
Opiates (yes)*	0.92 (0.82–1.03)	0.139	0.76 (0.67–0.86)	<0.001	0.76 (0.68–0.86)	<0.001
Chemotherapy (yes)*	1.07 (0.077–1.48)	0.677	1.05 (0.91–1.20)	0.509		
Antibiotics (total no.)	1.08 (1.05–1.11)	<0.001	1.03 (1.00–1.05)	0.030	1.03 (1.00–1.06)	0.097
Antibiotic days (days)	1.04 (1.03–1.05)	<0.001	1.02 (1.01–1.03)	<0.001	1.02 (1.02–1.03)	<0.001
Motility Agent (yes)*	1.19 (1.11–1.28)	<0.001	1.04 (0.98–1.10)	0.200		
Sorbitol (yes)*	1.08 (0.97–1.20)	0.162	1.06 (0.96–1.17)	0.225		
Suppository (yes)*	1.26 (1.15–1.37)	<0.001	1.13 (1.06–1.19)	<0.001	1.14 (1.06–1.22)	<0.001
Enteral Nutrition (yes)*	1.37 (1.26–1.50)	<0.001	1.23 (1.16–1.31)	<0.001	1.23 (1.16–1.31)	<0.001
Acid Suppressants (yes)	1.15 (1.03–1.30)	0.017	1.08 (0.94–1.23)	0.294		
Gastrointestinal comorbidities (yes)* **	1.09 (0.95–1.24)	0.225	0.98 (0.93–1.04)	0.507		
AIC	NA		0.982		0.982	

In this table we present independent predictors for diarrhea (WHO definition) using a generalized linear model, adjusting for age, sex, APACHE II Score, opiates, chemotherapy, number of antibiotics, antibiotic days, motility agent, sorbitol, suppository, enteral nutrition, acid suppressants, gastrointestinal comorbidities, and center. Total number of antibiotics reflects the number of unique antibiotics that a patient received

RR= Risk Ratio.CI=confidence interval. APACHE=Acute Physiology and Chronic Health Evaluation, AIC= Akaike Information Criterion

*Reference category is "no

**Celiac disease, Prior bowel resection surgery, Inflammatory bowel disease (Crohn disease, ulcerative colitis), Colectomy/Ileostomy, Chronic Pancreatitis, Gastroparesis, Diabetes

of the APACHE score and the differences were still very small. For example, a 10-year increase in age corresponds to a 1% increase in diarrhea and a 5-point increase in APACHE score corresponds to a 1% increase in risk of diarrhea.

Management modifications and consequences of diarrhea

The most frequent management modification prompted by diarrhea was holding a stool softener, and most frequent management consequence was ordering a CDI test (Table 3). After adjusting for age, sex, center and APACHE II score, diarrhea was associated with at least at least one management modification: discontinuing stool softener or pro-kinetic (RR 10.25, 95% CI 5.14–20.45, $p<0.001$) and fecal management devices (rectal bag applied or rectal tube inserted) or *C. difficile* testing (RR 6.16, 95% CI 3.4–11.17, $p<0.001$).

Clinical consequences of diarrhea

Patients with diarrhea (WHO definition) stayed in the ICU a median of 6.5 days (IQR 4, 12) in contrast to those without diarrhea who stayed 3.0 days (IQR 2, 4), $p<0.001$. Patients with diarrhea stayed in hospital 15 days (IQR 8, 31) compared to those without who stayed 7.0 days (IQR 3, 14), $p<0.001$). In the Cox regression competing risk model, diarrhea was not associated with death (HR 0.67; 95% CI 0.42–1.06; $p=0.086$). However, in the parametric models using the generalized gamma distribution, diarrhea was a predictor of ICU (HR 0.76; 95% CI 0.56–0.95; $p<0.001$) and hospital (HR 0.58; 95% CI 0.41–0.74; $p<0.001$) discharge, i.e., people with diarrhea were less likely to be discharged earlier. Model fit statistics are shown in the appendix (Appendix Table 5).

Table 3 Management modifications and consequences of diarrhea

Management modification and consequences	Patients with diarrhea* (*n* = 818)	No diarrhea (*n* = 291)	RR (95% CI)	*P* value
Any management modification, *n* (%)	166 (20.29)	5 (1.7)	10.25 (5.14–20.45)	< 0.001
Stool Softener held	118 (14.4)	4 (1.4)		
Feeds held	52 (6.4)	0 (0)		
Feeds changed	42 (5.1)	0 (0)		
Pro-kinetic held	21 (2.6)	1 (0.3)		
Any management consequence, *n* (%)	171 (20.9)	10 (3.4)	6.16 (3.4–11.17)	< 0.001
Clostridioides difficile-associated diarrhea test	94 (11.5)	6 (2.1)		
Other consequence	63 (7.7)	4 (1.4)		
Rectal tube inserted	37 (4.5)	4 (1.4)		
Rectal bag applied	17 (2.1)	2 (0.7)		

In this table, we present the management modifications and consequences of diarrhea (WHO definition) on individual management consequences

RR Risk Ratio

*Adjusted for age, sex, APACHE II score, center

Discussion

In this international multicenter prospective cohort study of 1109 critically ill patients, diarrhea was common, and the incidence varied based on the definition. Independent modifiable predictors for diarrhea included enteral nutrition, suppository use, and number of antibiotic days, while opioid use was associated with a lower occurrence of diarrhea. These predictors were consistent across definitions. Adjusted analyses found that diarrhea was associated with longer time to ICU and hospital discharge, but was statistically not associated increased hospital mortality.

Variation in bowel habit definitions [4] and inattention to usual bowel habits before critical illness make it challenging to identify what may be abnormal for a critically ill patient. A systematic review of constipation, diarrhea and the use of bowel protocols in the ICU identified 8 cohort studies examining diarrhea [5]. Most studies were retrospective or single-center, and used the definition applied in this study of 3 or more liquid bowel movements per day. DICE-ICU is the largest prospective multicenter study conducted with the primary focus on diarrhea in this setting; it also serves as an initial study examining the differences in stool assessment metrics and definitions. A previous single-center prospective study of 1300 critically ill patients examining a wide range of conditions contributing to gastrointestinal dysfunction (i.e. vomiting, diarrhea, bowel dilation, and gastric residuals) [17], documented only 14% as experiencing diarrhea [17], and found that having more than 2 gastrointestinal symptoms was associated with increased mortality and a longer length of ICU stay [17]. Our study focused on diarrhea specifically, rather than gastrointestinal dysfunction more generally, using 3 definitions.

We documented fair agreement across all diarrhea definitions applied. The WHO and the Bristol Stool Chart demonstrated moderate agreement. While the WHO definition was associated with the highest incidence of diarrhea, analyses yielded several consistent predictors across diarrhea definitions. The attributable morbidity and mortality of diarrhea across definitions was similar (data not shown). While there is no clear superior definition of diarrhea for critically ill patients, the WHO definition does encompass patients with diarrhea identified by the other definitions (Appendix Fig. 2). Ensuring consistent nomenclature in practice will improve inter-professional recognition of diarrhea at the bedside, and help to advance research in this field, including the testing effective interventions to prevent and treat diarrhea.

Our findings quantify and highlight the importance of antibiotic appropriateness and minimizing the number of antibiotic days for patients in the ICU. We showed that every additional day of antibiotic exposure is associated with a 10% increased risk of diarrhea per day, after adjusting for multiple antibiotics. Antibiotic stewardship programs may help to tailor antibiotic therapy and prevent indiscriminate prescribing; whether this reduces the burden of diarrhea remains to be evaluated [25, 26]. Our results are consistent with a prior study suggesting that diarrhea may often be iatrogenic in that antibiotics, suppositories, and enteral nutrition predispose critically ill patients to diarrhea [2]; our study helps to quantify the associated the risk.

While the enteral route is the preferred method of nutrition delivery in the ICU [27], it is often considered a cause of diarrhea, prompting discontinuation [13], which in turn may interrupt nutritional support. Preliminary data have shown an association between high protein

feeds and diarrhea compared to other types of enteral nutrition [28]. In our study, enteral nutrition was associated with the development of diarrhea. Post hoc analysis of nutritional composition suggested that high osmolality feeds or high fiber feeds were associated with diarrhea, rather than general exposure to enteral nutrition. Further research is needed on the association between diarrhea, different feeding formulae and feeding schedules (e.g., continuous or intermittent bolus).

This study documented several interventions that are initiated in response to diarrhea including altering or holding enteral nutrition, changing medications, investigating an infectious etiology, and rectal appliance management. These interventions have implications for patients and the health care system. If feeds are held frequently, this may exacerbate caloric and protein deficits. Frequent CDAD testing, although congruent with recent guidelines suggesting heightened awareness of this infection [29], incur laboratory and other costs related to contact isolation precautions for patients and clinicians until results are available.

We found that patients who experienced diarrhea had a longer stay in the ICU and hospital, but not an increased risk of death. Previous studies have yielded conflicting results regarding the association of diarrhea with increased mortality. In a recent systematic review of prospective studies of diarrhea in the ICU, an association between mortality and ICU and hospital length of stay was found; however, included studies had relatively small sample sizes, were at moderate risk of bias and the overall certainty of evidence was low [18]. Reasons for worse outcomes in patients with diarrhea seen in some studies may reflect changes in gut perfusion or altered gut microbiota during critical illness [30]. Translational research has shown reduced microbiome diversity in respiratory and gastrointestinal samples correlates with higher disease severity and adverse outcomes [31–34].

Limitations of our study include lack of mechanistic data to help explain the relationship between diarrhea and clinical outcomes. We cannot exclude the possibility of observer bias influencing patient management in response to diarrhea, or unmeasured confounders affecting analyses. The analyses of association do not indicate causation of course, and our goal was not to derive a diarrhea prediction model. Although our incidence of CDAD of 2.1% in this cohort is consistent with other ICU studies, CDAD testing was at the discretion of the ICU physician, which may lead to an underestimate of the incidence. We did not classify the appropriateness of antibiotics or analyze broad spectrum antibiotics in this study. Strengths of this study include the large sample size and heterogenous population allowing for detailed examination of predictors and outcomes. Our internal pilot study refined the study methods and calculation of the sample size for multivariable regression. We published our methods and analysis plan in a peer-review journal [19] enhancing the transparency of this report. We believe that the modifications to the protocol enhanced the robustness of these analyses. We enrolled consecutive, critically ill patients in both academic and community ICUs with international representation, enhancing the generalizability of the findings. Based on additional stakeholder input, we have presented our results as risk ratios instead of odds ratios (per protocol) to facilitate interpretability.

Our study may serve as a foundation for further work in refining a definition for diarrhea that is easily applied at the bedside. A universal validated definition of diarrhea in this population could be useful for inter-professional practice, to inform translational and clinical research on enteric infectious diseases, malabsorption, and gastrointestinal dysfunction. Future investigations should examine whether addressing modifiable predictors may prevent diarrhea and impact favorably on patient-important outcomes. Additional studies on gastrointestinal dysbiosis in critical illness may yield information on propensity to develop diarrhea and its attributable morbidity and mortality. Economic analyses would quantify the resources associated with diarrhea, which lead to bedside interventions by nurses, dieticians and pharmacists, diagnostic tests, and increased use of consumables, such as gowns and other personal protective equipment.

In conclusion, diarrhea is common among critically ill patients, and the incidence varies based on the definition employed. Modifiable diarrhea predictors include enteral nutrition and duration of antibiotic exposure. Further studies are needed to evaluate whether modifying these factors reduces the incidence of diarrhea, and to determine the impact on healthcare costs.

Supplementary Information

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The authors' roles are as follows. Conception and design: JCD, DJC, LM, WA Acquisition, analysis and interpretation of the data: JCD, DJC, LM, WA, KS, JWD, MD, PM, DA, LT, JM, JT, RC, RJ, AT, CH, TK, RC-C, MA, BR, WS, KB, WS, PL, TC. Analysis of the data: JCD, LM, DC. Drafting the manuscript: JCD, DC, LM, LT, JWD, MSD, JM, JT, AT. Critiquing the manuscript: JWD, KS, MD, PM, DA, LT, JM, JT, RJ, AT, CH, TK, RC-C, MA, WA, BR, WS, KB, WS, PL, TC. Final approval: All authors provided final approval of the manuscript.

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Upon request.

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Not applicable.

Declarations

Conflicts of interest
The authors have no competing interests to declare.

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References

1. Whelan K, Judd PA, Taylor MA (2004) Assessment of fecal output in patients receiving enteral tube feeding: validation of a novel chart. Eur J Clin Nutr 58:1030–1037
2. Ronan Thibault SG, Cler A, Delieuvin N, Heidegger CP, Pichard C (2013) Diarrhoea in the ICU: respective contribution of feeding and antibiotics. Crit Care 17:1–8
3. Reintam Blaser A, Malbrain ML, Starkopf J, Fruhwald S, Jakob SM, De Waele J, Braun JP, Poeze M, Spies C (2012) Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med 38:384–394
4. Schiller LR, Pardi DS, Spiller R, Semrad CE, Surawicz CM, Giannella RA, Krejs GJ, Farthing MJ, Sellin JH (2014) Gastro 2013 APDW/WCOG Shanghai working party report: chronic diarrhea: definition, classification, diagnosis. J Gastroenterol Hepatol 29:6–25
5. Hay T, Bellomo R, Rechnitzer T, See E, Ali Abdelhamid Y, Deane AM (2019) Constipation, diarrhea, and prophylactic laxative bowel regimens in the critically ill: A systematic review and meta-analysis. J Crit Care. https://doi.org/10.1016/j.jcrc.2019.01.004
6. Organization WH (2005) The treatment of diarrhoea: a manual for physicians and other senior health workers: 1–43
7. Lewis SJ, Heaton KW (1997) Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 32:920–924
8. Crobach MJ, Planche T, Eckert C, Barbut F, Terveer EM, Dekkers OM, Wilcox MH, Kuijper EJ (2016) European society of clinical microbiology and infectious diseases: update of the diagnostic guidance document for Clostridium difficile infection. Clin Microbiol Infect 22(Suppl 4):S63-81
9. Caroff DA, Edelstein PH, Hamilton K, Pegues DA, Program CDCPE (2014) The Bristol stool scale and its relationship to Clostridium difficile infection. J Clin Microbiol 52:3437–3439
10. Bliss D (2001) Reliability of a stool consistency classification system. Journal of WOCN 28:305–313
11. Zimmaro Bliss D, Dhamani KA, Savik K, Kirk K (2003) Tool to classify stool consistency: content validity and use by person of diverse cultures. Nurs Health Sci. https://doi.org/10.1046/j.1442-2018.2003.00145.x
12. Bishop S, Young H, Goldsmith D, Buldock D, Chin M, Bellomo R (2010) Bowel motions in critically ill patients:a pilot observational study. Criti Care Resuscit 12:182–185
13. Jack L, Coyer F, Courtney M, Venkatesh B (2010) Diarrhoea risk factors in enterally tube fed critically ill patients: a retrospective audit. Intensive Crit Care Nurs 26:327–334
14. Tirlapur N, Puthucheary ZA, Cooper JA, Sanders J, Coen PG, Moonesinghe SR, Wilson AP, Mythen MG, Montgomery HE (2016) Diarrhoea in the critically ill is common, associated with poor outcome, and rarely due to Clostridium difficile. Sci Rep 6:24691
15. Marcon AP, Amaral L, Carneiro V (2006) Nosocomial diarrhea in the intensive care unit. Braz J Infect Dis 10:384–389
16. Reintam A, Parm P, Redlich U, Tooding LM, Starkopf J, Kohler F, Spies C, Kern H (2006) Gastrointestinal failure in intensive care: a retrospective clinical study in three different intensive care units in Germany and Estonia. BMC Gastroenterol 6:19
17. Reintam A, Parm P, Kitus R, Kern H, Starkopf J (2009) Gastrointestinal symptoms in intensive care patients. Acta Anaesthesiol Scand 53:318–324
18. Taito S, Kawai Y, Liu K, Ariie T, Tsujimoto Y, Banno M, Kataoka Y (2019) Diarrhea and patient outcomes in the intensive care unit: systematic review and meta-analysis. J Crit Care 53:142–148
19. Dionne JC, Sullivan K, Mbuagbaw L, Takaoka A, Duan EH, Alhazzani W, Devlin JW, Duprey M, Moayyedi P, Armstrong D, Thabane L, Tsang JLY, Jaeschke R, Hamielec C, Karachi T, Cartin-Ceba R, Muscedere J, Alshahrani MSS, Cook DJ (2019) Diarrhoea: interventions, consequences and epidemiology in the intensive care unit (DICE-ICU): a protocol for a prospective multicentre cohort study. BMJ Open 9:e028237
20. Dionne JC, Sullivan K, Mbuagbaw L, Al-Hazzani W, Karachi T, Hamielec C, Tsang J, Takaoka A, Cook DJ (2016) Tu1068 diarrhea in the intensive care unit: epidemiology (The DICE Study). Gastroenterology. https://doi.org/10.1016/S0016-5085(16)32815-3
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S (2008) The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 61:344–349
22. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
23. Cummings P (2009) Methods for estimating adjusted risk ratios. Stand Genomic Sci 9:175–196
24. StataCorp. (2019) Statistical Software: Release 16
25. Lindsay PJ, Rohailla S, Taggart LR, Lightfoot D, Havey T, Daneman N, Lowe C, Muller MP (2019) Antimicrobial stewardship and intensive care unit mortality: a systematic review. Clin Infect Dis 68:748–756
26. Pickens CI, Wunderink RG (2019) Principles and practice of antibiotic stewardship in the ICU. Chest 156:163–171

27. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C, Society of Critical Care M, American Society for P, Enteral N (2016) Guidelines for the provision and assessment of nutrition support therapy in the adult critically Ill patient: society of critical care medicine (SCCM) and american society for parenteral and enteral nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 40:159–211
28. Dionne JC, Campbell T, Janisse N, Zytaruk N, Saunders L, Heels-Ansdell D, Francois L, Johnstone J, Cook DJ (2020) Effect of fiber, osmolarity, and protein content of enteral nutrition on the development of diarrhea in critical illness. Gastroenterology. https://doi.org/10.1016/S0016-5085(20)33157-7
29. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, Dubberke ER, Garey KW, Gould CV, Kelly C, Loo V, Shaklee Sammons J, Sandora TJ, Wilcox MH (2018) Clinical practice guidelines for clostridium difficile infection in adults and children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 66:e1–e48
30. McDonald D, Ackermann G, Khailova L, Baird C, Heyland D, Kozar R, Lemieux M, Derenski K, King J, Vis-Kampen C, Knight R, Wischmeyer PE (2016) Extreme dysbiosis of the microbiome in critical illness. mSphere. https://doi.org/10.1128/mSphere.00199-16
31. Lankelma JM, van Vught LA, Belzer C, Schultz MJ, van der Poll T, de Vos WM, Wiersinga WJ (2017) Critically ill patients demonstrate large interpersonal variation in intestinal microbiota dysregulation: a pilot study. Intensive Care Med 43:59–68
32. Lamarche D, Johnstone J, Zytaruk N, Clarke F, Hand L, Loukov D, Szamosi JC, Rossi L, Schenck LP, Verschoor CP, McDonald E, Meade MO, Marshall JC, Bowdish DME, Karachi T, Heels-Ansdell D, Cook DJ, Surette MG, P Canadian Critical Care Trials G, Canadian Critical Care Translational Biology G (2018) Microbial dysbiosis and mortality during mechanical ventilation: a prospective observational study. Respir Res 19:245
33. Iapichino G, Callegari ML, Marzorati S, Cigada M, Corbella D, Ferrari S, Morelli L (2008) Impact of antibiotics on the gut microbiota of critically ill patients. J Med Microbiol 57:1007–1014
34. Iapichino G, Lankelma JM, Joost Wiersinga W (2017) Gut microbiota disruption in critically ill patients: discussion on "Critically ill patients demonstrate large interpersonal variation of intestinal microbiota dysregulation: a pilot study." Intensive Care Med 43:718–719