DIARRHEA DURING CRITICAL ILLNESS

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ABSTRACT

Diarrhea is common during critical illness; however, the etiology, definitions, incidence and risk factors for diarrhea and its impact on patient important outcomes require further investigation. There are many possible etiologies of diarrhea, including iatrogenic causes such as laxative medications, often administered as part of bowel protocols, as well as *Clostriodiodes difficile* associated diarrhea (CDAD).

This thesis includes 6 chapters that address the knowledge gaps in the literature regarding the epidemiology of diarrhea in the intensive care unit (ICU), the impact of bowel protocols on diarrhea, and CDAD in critically ill adults.

Chapter 1 provides an introduction to gaps in the literature that are addressed by the studies included in this thesis.

Chapter 2 outlines the methodology used to inform the protocol for the Diarrhea, Incidence, Consequences and Epidemiology in the Intensive Care Unit (DICE-ICU) Study.

Chapter 3 reports on the findings of DICE-ICU including the incidence, risk factors, definitions, and outcomes of patients who develop diarrhea in the ICU.

Chapter 4 provides a content analysis of bowel protocols used in multiple ICUs.

Chapter 5 summarizes a nested cohort study addressing the incidence, prevalence, timing, treatments, and outcomes of CDAD in critically ill patients enrolled in the PROSPECT Trial.

Chapter 6 summarizes the work and discusses the strengths and limitations, implications and conclusions presented in this PhD thesis.

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I dedicate this dissertation to my Mum and Dad, Helen and Robert Dionne. I also dedicate this in loving memory of Roger Legon.

CONTRIBUTIONS BY OTHERS

At the end of each chapter is a full account of authors’ contributions.

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LIST OF ABBREVIATIONS

ACG= American College of Gastroenterology

AIC= Akaike information criteria

APACHE II= Acute Physiology and Chronic Health Evaluation II Score

Bliss= Bliss Stool Classification System

Bristol= Bristol Stool Chart

CAG= Canadian Association of Gastroenterology

CCCTG= Canadian Critical Care Trials Group

CDAD= *Clostridioides difficile* associated diarrhea

CDI = *Clostridioides difficile* infection

CI= Confidence Intervals

CIHR= Canadian Institute for Health Research

DICE-ICU= Diarrhea, Interventions, Consequences and Epidemiology in the Intensive Care Unit study

ELISA= Enzyme Linked Immunosorbent Assay

EN= Enteral Nutrition

ESCMID= European Society of Clinical Microbiology and Infections Disease

ESICM= European Society of Intensive Care Medicine

H2RA= Histamine-2 Receptor Agonists

HR= Hazard Ratio

IDSA= Infectious Diseases Society of America

ICU= Intensive Care Unit

IQR= Interquartile Range

LAMP= Loop Mediated Isothermal Amplifications

LOS= Length Of Stay

MD= Mean Difference

NAAT= Nucleic Acid Amplification Test

OR=Odds Ratio

PCR= Polymerase Chain Reaction

PEG= Polyethylene Glycol

PPI= Proton Pump Inhibitor

PROSPECT=Probiotics to prevent Severe Pneumonia and Endotracheal Colonization Trial

PSI= Physicians Services Incorporated

RCT= Randomized Controlled Trials

RMA= Regional medical Associates

RR= Risk Ratio

SD= Standard Deviation

SHEA= Society for Healthcare Epidemiology of America

STROBE= Strengthening The Reporting of Observational Studies in Epidemiology

VAP= Ventilator Associated Pneumonia

WHO= World Health Organization

CHAPTER 1 - Introduction

1.1 Background

Critical illness results in dysregulation of many organ systems; however, optimization of cardio-pulmonary function and normalization of hemodynamics often supersedes the management of gastrointestinal dysfunction in this setting and the impact of critical illness on gastrointestinal function remains under-investigated.

Gastrointestinal dysfunction can include issues ranging from vomiting, feeding intolerance and diarrhea to constipation and ileus[1]. These symptoms are common in the intensive care unit (ICU) and are frequent concerns discussed on medical rounds. However, how the interdisciplinary team defines, monitors, and intervenes to address each of these issues is variable. To meet the needs of critically ill patients experiencing gastrointestinal dysfunction, research has sought to examine different aspect of this dysfunction and its prevention and treatment including the determination of risk factors for diarrhea, the development of protocols to mitigate constipation and feeding intolerance and the definition, diagnosis and treatment of *Clostridioides difficile* associated diarrhea (CDAD). This thesis aims to address the gaps in the literature surrounding those issues, including the development and execution of a large international study on the risk factors and consequences of diarrhea in critical illness; performing a content analysis of bowel protocols in the ICU; and conducting a cohort study of CDAD in a large population of critically ill patients.

The remainder of this chapter lays down the context of each of the issues addressed in this thesis, outlining what we know, where the gaps in knowledge exist, and how the thesis attempts to fill the gaps in subsequent chapters 2-5.

1.2 Diarrhea in the critically ill patients

Many challenges exist in investigating diarrhea in the critically ill, including inattention to the problem, variations in definitions applied across studies, and inconsistent research findings on the impact of diarrhea on patient important outcomes. This has had a direct impact on estimating the incidence of prevalence of this problem in the ICU.

The incidence of diarrhea in the ICU has ranged in the literature from 2%-95% [2-4]. This wide variation may in part be to a lack of consistent definitions applied across studies, and ineffective metrics in monitoring patient's bowel habits in the ICU. A systematic review by Hay and colleagues 2019[4] reported that definitions used across studies were variable. Three of 8 studies reported that diarrhea was associated with a greater length of ICU stay, while only 1 of the 8 studies reported a higher mortality[4]. Half of the studies were retrospective cohorts, and only 1 was multicentre [4].

Taito and colleagues[5] performed a systematic review of diarrhea in the ICU examining short term outcomes including ICU and hospital mortality, and length of stay. The authors identified 12 studies including a total sample size of 13,140; 8 of the 12 studies were prospective cohort designs[5]. This meta-analysis found that diarrhea was associated with an increased risk of ICU mortality (risk ratio [RR] 1.43, 95%CI 1.00,1.98), as well as greater lengths of ICU stay (RR 8.08, 95%CI 5.85,10.32) and total hospital stay (RR 9.67, 95%CI 2.17,17.16)[5].

With differences in definitions used, incidence and prevalence reported, and variable findings addressing patient important outcomes associated with diarrhea in the ICU, I designed a multicenter, multinational prospective cohort study to address these

gaps in the literature – the Diarrhea, Incidence, Consequences and Epidemiology in the intensive care unit (DICE-ICU) Study. Specifically, the objectives were to determine the true incidence of diarrhea, assess risk factors for diarrhea, validate a definition of diarrhea in this patient population, and determine its impact on patient outcomes. In this thesis, I will summarize the design and results of this study in 2 separate chapters. In Chapter 2, I will present the protocol for the Diarrhea, Interventions, Consequences and Epidemiology in the Intensive Care Unit (DICE-ICU) Study and, in Chapter 3, I will present the results of the DICE-ICU Study.

1.3 Bowel Protocols in the Intensive Care Unit

Bowel protocols are increasingly being used in the ICU to minimise feeding intolerance and constipation. However, the evidence about whether bowel protocols are beneficial or positively influence patient important outcomes is conflicting. A systematic review of bowel protocols in the ICU [6] identified 4 trials of 534 critically ill patients examining their impact on constipation, feeding intolerance and duration of mechanical ventilation. The interventions tested in the 4 trials included lactulose or polyethylene glycol (PEG) compared to usual care or placebo. The results of this meta-analysis showed that bowel protocols were associated with no reduction in feeding intolerance (RR 0.94, 95%CI 0.62-1.42), constipation (RR 0.50, 95%CI 0.25,1.01) or days of mechanical ventilation (mean difference (MD) 0.01 days, 95%CI –2.67,2.69 days) based on low certainty of evidence [6].

An updated systematic review and meta-analysis [4] examining constipation, diarrhea and bowel protocols in the ICU identified 6 studies, including 3 trials and 3 prospective cohort studies. The studies varied in terms of the laxatives used, including

senna, lactulose, PEG or glycerine compared to placebo, or usual care. The authors found similar results to Oczkowski and colleagues[6]; bowel protocols did not decrease constipation (RR 0.39, 95%CI 0.14,1.05) or duration of mechanical ventilation (weighted MD 0.18, 95%CI –3.25,3.61), but did result in an increased risk of diarrhea (weighted MD 1.58, 95%CI 1.22,2.04). Hays and colleagues[4] did not find a difference in length of ICU stay (weighted MD -0.76, 95%CI –2.27,0.75) or mortality (RR 0.83, 95%CI 0.56,1.22) associated with bowel protocols.

With the growing use of bowel protocols, evidence currently showing no benefit of bowel protocol regimens, and their potential to induce diarrhea, I performed a content analysis of bowel protocols in an international sample of ICUs which were participating in a randomized controlled trial of the probiotic *Lactobacillus rhamnosus GG* compared to placebo. The Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial (PROSPECT) found no effect for bowel protocols in preventing ICU acquired infections including ventilator associated pneumonia (VAP), other nosocomial infections, or diarrhea [NCT02462590}[7]. The objective of the study was to analyze the use of bowel protocols in clinical practice in centers participating in the trial, specifically, describing the initiation, medications used, escalation approaches, discontinuation criteria, stool assessment methods and contraindications. In chapter 4, I will summarize the design and results of this study.

1.4 CDAD in the Intensive Care Unit

Clostridioides difficile infection (CDI) is associated with significant morbidity and mortality in hospitalized patients [8], including ICU patients who are at an increased risk of contracting the infection [9]. CDI is associated with significant costs to the healthcare

system. Costs of $8,911 USD to $30,049 USD [10] for patients with CDI, with an annual estimated cost of 1.1 to 3.2 billion USD per year [11] for CDI associated care. ICU CDI costs have been demonstrated to be as high as $11,353 USD compared to $6,028 for patients who do not have CDI [11]. Given the impact on patient outcomes and costs to the system, CDI remains a research priority.

As highlighted previously, diarrhea is common in the ICU, and increases a patient's risk of skin breakdown and dehydration. Although the etiology of diarrhea in this patient population is multifactorial [9, 12], the most concerning diagnosis is CDAD. Common symptoms associated with CDAD, including pain, fever, and leukocytosis [9, 13], may be either masked in the ICU patient, or be contributed to other disease processes, making the diagnosis of CDAD challenging. This can result in unnecessary testing for CDAD and unnecessary contact precautions from an infection control perspective, which may limit patient contact with health care providers and family members, with diverse attendant consequences.

Risk factors for CDAD include antibiotic exposure, morbid state, age, mechanical ventilation, length of stay and acid suppression exposure [9]. Although the effect of some of these predisposing factors such as acid suppression on the risk of CDI is debated, many of these risk factors are frequent in ICU patients[9, 14, 15].

Timing of development of CDAD and quantifying the true incidence of CDAD in the ICU remains a gap in the CDAD literature, as most studies conducted in this population are comprised of retrospective cohorts and cross-sectional studies. More research is required to describe the proportion, including incidence and prevalence, of

patients who develop CDAD prior, during or after ICU admission and its impact on patient important outcomes including mortality.

Severity of CDAD can range from mild to severe complicated CDAD. Different scores exist to determine the severity based on different clinical factors, including the Infectious Disease Society of American (IDSA)[16], the American College of Gastroenterology (ACG)[17] and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)[18]. Without an ICU specific definition for CDAD, there is not a gold standard for defining severity in this population either. Therefore, I sought to assess the severity of CDAD using these 3 accepted scoring systems in the critically ill. In chapter 5, I will summarize the design and results of this study to determine the incidence, prevalence, severity, timing and treatment of CDAD in the ICU within a nested cohort study with of the PROSPECT trial.

1.5 Conclusions

In Chapter 6, I will summarize the work of this dissertation, strengths and limitations including methodologic challenges, and future work in this research area.

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CHAPTER 2:
Diarrhea: Interventions, Consequences and Epidemiology in the Intensive Care Unit: (DICE-ICU) – A protocol for a Prospective Multicenter Cohort Study (Published *BMJ Open* 2019;**9**:e028237)

Diarrhea: Interventions, Consequences and Epidemiology in the Intensive Care Unit:

(DICE-ICU)—A Protocol for a Prospective Multicenter Cohort Study

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Abstract

Introduction

Diarrhea is a frequent concern in the Intensive Care Unit (ICU) and is associated with prolonged mechanical ventilation, increased length of ICU stay, skin breakdown and renal dysfunction. However, its prevalence, etiology, and prognosis in the critically ill have been poorly studied. The primary objectives of this study are to determine the incidence, risk factors, and consequences of diarrhea in critically ill adults. The secondary objectives are to estimate the incidence of *Clostridium difficile*-associated diarrhea (CDAD) in ICU patients and to validate the Bristol Stool Chart and Bliss Stool Classification System characterizing bowel movements in the ICU. Our primary outcome is diarrhea. Our secondary outcomes include: CDAD, ICU and hospital mortality, and ICU and hospital length of stay.

Methods and analysis

This international prospective cohort study will enroll patients over 10 weeks in 12 ICUs in Canada, the United States, Poland, and Saudi Arabia. We will include all patients 18 years of age and older who are admitted to the ICU for a least 24 hours and follow them daily until ICU discharge. Our primary outcome is the incidence of diarrhea based on the World Health Organization (WHO) definition, during the ICU stay. Our secondary outcomes include: CDAD, ICU and hospital mortality, and ICU and hospital length of stay. We will use logistic regression to identify factors associated with diarrhea (as defined using WHO criteria) and the kappa statistic to measure agreement on diarrhea rates between the WHO definition and the Bristol Stool Chart and Bliss Stool Classification System.

Ethics and dissemination

The protocol has been approved by the research ethics board of all participating centers. The DICE-ICU Study will generate evidence about diarrhea and its frequency, predisposing factors, and consequences, to inform critical care practice and future research.

Lay Summary

Diarrhea is a frequent clinical problem for hospitalized patients including those who are critically ill in the ICU. Diarrhea can cause complications such as skin damage, dehydration, and kidney problems. It is not clear how common diarrhea is in the ICU, the factors that cause it, or the best way for clinicians to assess it. The DICE-ICU study is an international prospective observational study to examine the frequency, risk factors and outcomes of diarrhea during critical illness.

Funding

DICE-ICU has received funding from Physician's Services Incorporated (PSI), the Canadian Association of Gastroenterology (CAG), Hamilton Regional Medical Associates (RMA) and the Canadian Institutes for Health Research (CIHR).

Article Summary

Strengths and Limitations of this Study

Strengths

- Large prospective, international, multicenter, cohort study of a mixed population of critically ill adults.
- Comprehensive evaluation of diarrhea incidence and its potential risk factors throughout the ICU stay.
- Bedside nurse characterization of all bowel movements with the WHO definition, Bristol Stool Chart and Bliss Stool Classification System to validate these scoring tools in critically ill adults.

Limitations

- Possible missing data to characterize some bowel movements.
- Possible reporting bias or observer bias influencing some data collection.

Introduction

The reported incidence of diarrhea among critically ill patients ranges from 2% to 95% [1, 2]. This wide range is due to the lack of a universally accepted definition in the intensive care unit (ICU). It is often difficult to differentiate true diarrhea (the passage of more than 3 liquid bowel movements per 24 hours) from a change in stool frequency or stool consistency (e.g., looser stools). There is also wide variation in what is considered 'a normal bowel habit' [3], ranging from 2-3 bowel movements per day to 3 bowel movements per week. Such 'normal variation' makes it challenging to define diarrhea and to identify what may be 'abnormal' in the ICU setting. The concept of what constitutes a normal bowel pattern in the ICU has not been well studied. The ideal definition of diarrhea in the ICU remains unclear.

The World Health Organization (WHO) defines diarrhea as the passage of 3 or more liquid stools per day[4]. While simple, and easily applied at the bedside, clinicians rarely refer to this definition in ICU practice. A criticism of the WHO definition is that quantification of stool is not necessarily an accurate indicator of colonic transit time. The most recognized stool evaluation instrument in hospitals is the Bristol Stool [5], comprising 7 categories with a graphical depictions and text descriptions for each category. A Bristol Score of 6 or 7 is classified as diarrhea [6]. The Bristol Stool Chart is a better predictor of whole-intestinal transit time than stool frequency [5]. The Bristol Stool Chart has subsequently been used to define diarrhea by the European Society for Clinical Microbiology and Infectious Disease, and has used the Bristol Stool Chart to define diarrhea for *Clostridioides difficile* infection [7].

The Bliss Stool Classification System is an alternative system initially developed to assess stool consistency in patients with fecal incontinence. The tool has 4 categories with depictions and descriptions and can be applied at the bedside, but with fewer categories; it has a good reliability when used by health care professionals, nursing students and volunteers [8]. Further reliability and validity testing has been performed [8, 9], though this instrument has not been as widely used in research. There are no studies that validate the Bristol Stool Chart or the Bliss Stool Classification System in the ICU setting for either clinical or research purposes.

Antibiotics, antifungal therapy, prokinetics and enteral nutrition may predispose to diarrhea in the critically ill [2]; however, the risk of diarrhea associated with these factors is unclear and poorly quantified due to the retrospective designs and small sample sizes of previous studies. Without strong evidence informing ICU clinicians of the possible etiologies of diarrhea, enteral nutrition is often considered the culprit, and feeds are discontinued [10, 11]. While the enteral route is the preferred method of nutrition delivery in the ICU [12], if diarrhea is misattributed to enteral nutrition, unnecessary feeding interruption may exacerbate caloric and protein deficits.

Studies on the epidemiology of diarrhea in critically ill patients are limited. These studies have explored issues of gastrointestinal failure (e.g., feeding intolerance, gastrointestinal hemorrhage, and ileus) [13], diarrhea in enterally fed critically ill patients [10], or risk factors of diarrhea [14, 15]. Research designs to

date have included database registry studies [15], case-control studies [14], and retrospective audits. Interest in diarrhea has become particularly relevant as enteral nutrition, often considered the cause of diarrhea in the ICU, is used earlier and more often than in the past. Furthermore, there is growing concern about *Clostridioides difficile* associated diarrhea (CDAD) in this setting.

We are conducting a prospective multicenter study with the following objectives: to determine the incidence and frequency of diarrhea, risk factors for diarrhea and consequences (ICU and hospital mortality, ICU and hospital length of stay) of diarrhea in critically ill adults and validate different stool classification systems. The primary outcomes are to determine the frequency and the incidence of diarrhea, defined using the WHO criteria and risk factors for diarrhea in this patient population. The secondary outcomes are to estimate the incidence of CDAD in ICU patients, validate the Bristol Stool Chart and Bliss Stool Classification System for characterizing bowel movements, ICU and hospital mortality, and ICU and hospital length of stay.

Methods and Analysis

Design

The DICE-ICU Study is a 10-week prospective cohort study of consecutively admitted critically ill patients, and will be conducted at 12 academic and community medical and surgical ICUs in Canada, the United States, Poland, and Saudi Arabia.

Participants

We will include all consecutive patients of 18 years of age or older admitted to the ICU for at least 24 hours, regardless of their mechanical ventilation status. There are no exclusion criteria except patients admitted to the ICU for < 24 hours. At centers with multiple ICUs, we will enroll patients in medical, surgical and mixed ICUs rather than specialized ICUs (e.g., cardiovascular surgery units). In each participating ICU, we will document several center-level variables including the number of ICU and hospital beds, population case-mix, unit design, university affiliation, and use of a 'bowel protocol' (an established order set of prescribed laxatives and/or motility agents with parameters that describe when to use these medications for patients who have not had a bowel movement)[16] .

Patient and Public Involvement

Our protocol did not have a patient or patient family member engagement in its development of the research question, ascertainment of outcomes or methodology. Our population of interest is critically ill patients who are either mechanically ventilated, comatose or have altered level of consciousness due to their underlying critical illness condition or associated sedation. Such patient characteristics which typically persist for the majority of their ICU admission preclude meaningful real-time patient engagement as the study progresses. However, our ethics review board includes patient representatives who provided input to the design of the protocol and its implementation. Also, we will disseminate the results of the study to patients, families and citizens

through multimedia methods including pamphlets, social media and research boards in the ICU setting.

Enrolment

Daily, research coordinators will screen all newly admitted patients to each participating ICU who will also document the prior location (e.g., emergency department, operating room, medical or surgical ward), hospital and ICU admission dates. The research coordinators will collect baseline patient characteristics including age, sex and chronic comorbidities (pre-hospital), and Acute Physiology and Chronic Health Evaluation II (APACHE II) score and admitting diagnosis (at ICU admission). Conditions associated with an increased risk for diarrhea (e.g., gastrointestinal bleeding, history of short bowel syndrome, inflammatory bowel disease, history of *Clostridioides difficile* infection, and the presence of ileostomy or colostomy) or a decreased risk of diarrhea (e.g., opiates) (pre-ICU period) will also be documented.

Outcomes

We will perform prospective daily data collection until death in the ICU or ICU discharge. Daily, the bedside nurse will use the case report form refined during the DICE Pilot Study [17] to track all stools. The number and character of each stool will be documented daily using the WHO Definition and the Bristol Stool Chart and Bliss Stool Classification System. We will use these data to ascertain our primary outcome of the incidence and frequency of diarrhea in the study population over a 10 week

period in participating ICUs.

Research coordinators will collect data daily, completing a standardized, previously piloted and refined case report form (CRF)[17]. The CRF (Appendix 1) includes data on: life support utilization (mechanical ventilation, vasopressor usage, renal replacement therapy), laboratory values, physiotherapy, and clinical outcomes. Research coordinators will also document whether nutrition was administered, nutrition formulation, administrative route (enteral or parenteral), infusion rate, and any feeding interruption that may be risk factors for diarrhea (primary outcome). We will document nutritional targets as determined by the ICU dietitians and whether target rates are met. Research coordinators or bedside pharmacists will also track relevant medications (e.g., antibiotics, acid suppressants, antifungal agents, prokinetics, opioids, laxatives and hyperosmolar medications) that may be risk factors for diarrhea (primary outcome). Research coordinators will document the consequences of diarrhea such as electrolyte abnormalities, use of anti-diarrheal agents, use of fecal management devices, and diagnostic test ordering (e.g., for *Clostridioides difficile*, malabsorption etc). Research coordinators will collect detailed data on all patients developing CDAD (secondary outcome). We will also document the length of ICU (secondary outcome) and hospital stay (secondary outcome and mortality (ICU and hospital) on all patients enrolled in the study (secondary outcomes).

Data Management

The research coordinator at each site will enter the data locally into a web-

based system (iDatafax, version 4.3.0, 2013) [18]. A Data Manager at the McMaster University DICE-ICU Methods Center will validate all data, ensuring that ambiguous, out of range or missing data are identified and addressed in a timely manner. We will make every attempt to resolve missing data by querying participating centers. If data remain missing, we will address this with the multiple imputation methods, based on the type and distribution of missing data.

Training of Sites

Research coordinators at each site will be oriented by the principal investigator to the data collection forms though site initiation visits in-person or by webinar, and standard operating procedures. At each site, bedside nurses will be oriented to the stool classification systems and trained by the research coordinator on how to record the patient's bowel movements on the case report forms at scheduled sessions and at the bedside. Throughout the study, the Methods Center Data Manager will also give suggestions and feedback to the site research coordinators on data collection to ensure protocol fidelity and uniformity across sites.

Central Adjudication

In duplicate, two independent adjudicators will review all possible cases of CDAD. Patients who have a possible *Clostridium difficile* infection will be adjudicated using the Infectious Disease Society of America criteria [19]. For all possible cases, the following will also be adjudicated: stool frequency,

complications (e.g., colectomy), treatments (antibiotics, surgery), and overall severity according to guidelines of the European Society of Clinical Microbiology and Infectious Diseases [20] , Infectious Disease Society of America [19] and American College of Gastroenterology [21].

Sample size

Our sample size estimation is based on two approaches. The first is the standard rule of thumb approach which is based upon the independent factors under examination (in our 4-center DICE Pilot Study, there were 8 independent risk factors for diarrhea) and the number of events required for each degree of freedom which requires 20 events per factor. Using this approach, with 8 independent risk factors and 7 degrees of freedom, we would require 140 patients with diarrhea to examine these factors in a multivariate analysis [22]. Our second approach derives the sample size based upon our DICE Pilot Study with the primary objective of determining independent factors associated with diarrhea during critical illness. We have used the results of our DICE Pilot Study in which antibiotic exposure (main independent variable) was associated with diarrhea (adjusted odds ratio [OR] 2.15 95% CI 1.04-4.4) in the logistic regression to justify the sample size. Our sample size is computed for the research question that would require the largest sample size (which is the diarrhea risk factor analysis), inherently providing sufficient power to address the other objectives. In the DICE Pilot Study, we included the following variables: age, sex, APACHE II Score, and use of relevant drugs (e.g., motility modifiers, stool softeners). Among the 268 patients (80% of total population)

exposed to antimicrobials, 182 (67%) had diarrhea. Among the 67 patients not exposed to antimicrobials, only 19 (28%) had diarrhea (crude OR of 5.34; 95% CI 2.96 – 9.64). We have computed sample sizes for a range of plausible effect sizes (based on confidence intervals from the DICE Pilot Study). Approximately 1000 patients are required to detect an OR as small as 1.6 at level of significance $\alpha=0.05$ and power $(1-\beta)= 0.8$, if 80% of the total population is exposed to antimicrobials (computations by G Power Version 3.1.9.2)[23]. Given the consideration of both approaches, this study will be adequately powered to answer our primary research questions and adequately explore risk factors for diarrhea. Given the observational design, the ultimate sample size will be determined by the number of patients admitted to the ICU in participating centers during the study period; we will target at least 1,000 critically ill adults.

Data Analysis

Analysis will include descriptive and inferential statistics. We present our detailed statistical plan for evaluation of the primary and secondary outcomes in Table 1. We will report baseline characteristics, that will be described using counts (percentage) for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables as appropriate. Our primary outcome will be defined by WHO criteria of $\geq$3 liquid bowel movements/day, and additional definitions of diarrhea including a Bristol Stool Chart Score of 6 or 7, and Bliss Stool Classification System score of 4 will also be reported. The incidence of diarrhea will be computed as the number of new cases during ICU stay divided by the person-time at

risk. We will also report the frequency of diarrhea defined as the proportion (the number of patients who have developed diarrhea/the number of patients within the DICE-ICU cohort) of patients with new ICU-acquired diarrhea and will be computed for all 3 definitions.

The role of covariates (e.g., age, sex, APACHE II Score, drugs, prior gastrointestinal disease) in the occurrence of diarrhea will be analyzed with a logistic regression model that we developed during the DICE Pilot Study [17]. The consequences of diarrhea (time to ICU and time to hospital discharge) will be described and assessed using Cox regression; the influence of diarrhea on mortality will be assessed using logistic regression techniques. In these models, covariates will be entered as a block. Goodness-of-fit will be assessed by examining the residuals for model assumptions and using the Hosmer and Lemeshow goodness-of-fit test. Odds ratios (or hazard ratios), 95% confidence intervals and p-values will be reported.

For the validation of the Bristol Stool Chart and Bliss Stool Classification System we will use the WHO definition of diarrhea as the reference standard. We will compute agreement between the WHO definition of diarrhoea and the Bristol Stool Chart first; and then the Bliss Stool Classification System diarrhoea, using the Kappa statistic.

All analyses will be performed with SPSS software (version 22.0, 2013)[24].

Ethics and Dissemination

We have received local research ethics approval for the DICE-ICU Study in all participating centers. There are no safety concerns for enrolled patients. Information privacy will be addressed by de-identified data that is stored in password-protected computers in locked research offices at each center. There is a waiver of informed consent for this observational, non-interventional study in all centers except one that required written informed consent.

The results of this study will be disseminated by presenting the findings locally at each participating hospital, as well as nationally and internationally at critical care and gastroenterology conferences. Findings will be shared with interested national societies crafting guidelines in critical care. We will publish the results in a peer-review journal.

Discussion

On daily ICU rounds, diarrhea is discussed and addressed by a multidisciplinary team of clinicians - nurses, physicians, pharmacists and dietitians - and sometimes by concerned family members. Better understanding of the prevalence, characterization, risk factors and consequences of diarrhea will inform patient care for each of these professionals. Strategies initiated by each group could be implemented to prevent or treat diarrhea, in turn decreasing complications such as skin breakdown, electrolyte abnormalities, and nutritional deficiencies. For example, pharmacists may suggest changing medications; dietitians may modify feeding solutions; nurses may insert fecal management devices; families and bedside clinicians may increase the use of

protective materials and devices when entering the patient's room. Clinicians need to understand whether these interventions provide any benefit, cause any harm, and whether their cost is justified by the expected consequences associated with their use.

The burden of illness of diarrhea for patients appears to vary based on the definition used, highlighting the importance of making the definition explicit when citing incidence rates. The DICE-ICU Study will employ the 3 simplest measurement tools for diarrhea that are candidates for use in the busy ICU setting (the WHO definition, Bristol Stool Chart, and Bliss Stool Classification System). Clinicians perceive a high burden of illness and workload associated with diarrhea in the ICU [25]. Patients with diarrhea often have extensive work-ups to identify the underlying etiology of diarrhea. The European Society of Intensive Care Medicine (ESICM) Working Group on Abdominal Problems (2012) emphasizes that more research is required to identify the mechanism of diarrhea in critically ill patients, to identify different phenotypes of diarrhea, and thus, potential therapies[26].

A mechanism of interest for diarrhea includes alteration in the gut microbiota during critical illness. A study by Iapichino and colleagues [27, 28] demonstrated in 15 critically ill patients who had not been exposed to antibiotics or steroids prior to ICU admission had a reduction in intestinal anaerobes with an increase in *Enterococcus* isolates. Interestingly, 12 of the 15 patients developed diarrhea and were also found to be negative for CDI [27]. A recent pilot prospective cohort study examined changes in fecal microbiota in 34 septic and non-septic critically ill patients in centers where systematic decontamination of the digestive tract (SDD) is used compared to 15 healthy controls [29]. The authors found low diversity of

species in the critically ill patient cohort compared to healthy controls including loss of *Faecalibacterium, Pseudobutryivibrio, Ruiminococcus, Subdoligranulum [29]*. There was also an increase of >75% of one genus in 4 of the 34 patients with *Enterococcus, Staphylcoccus*, *Escherichia* and *Shigella* in the critically ill patients which was not seen in the healthy controls cohort [29]. In this cohort there was no CDI infection; however, it is unclear if these patients had diarrhea during admission. These studies highlight the importance of future research into the microbiota during critical illness and how this may influence a patient's propensity to develop diarrhea.

While many reasons for diarrhea exist in the ICU, infectious etiologies are of particular concern. Although CDAD is a common concern, only a small percentage (11%) of patients with diarrhea are found to have CDAD [30]. The prevalence of CDAD in ICU patients is approximately 2% across a variety of ICUs, based on a recent systematic review of 16 retrospective and 6 prospective studies [30]. To date, there are only 4 prospective cohort studies focusing on ICU-acquired CDAD describing 92 patients [31-33] [34]. Patients with ICU-acquired CDAD appear to have an increased length of ICU and hospital stay compared to patients without CDAD [35]. However, this lack of high quality, observational data establishing the prevalence of ICU-acquired CDAD can lead to over-investigation, over-treatment, and over-attribution of diarrhea to this infection, potentially delaying the diagnosis of the true etiology of diarrhea. DICE-ICU will contribute to the growing knowledge of the prevalence of ICU-acquired CDAD. Data generated on the probability of various other etiologies of diarrhea in the DICE-ICU Study will offer probabilities associated with

each differential diagnosis, and may help to rationalize common, sometimes unnecessary resource-intensive investigations when seeking the root cause of diarrhea.

A more detailed understanding of diarrhea in the ICU will also help to refine approaches to care for patients with this problem. Future research may also illuminate whether diarrhea decreases physical contact with patients (e.g., pre-emptive isolation of patients associated with less frequent examination by physicians, and shorter visits by clinicians and families).

DICE-ICU has several strengths. It is a large prospective cohort study that encompasses both academic and community ICUs around the world. The study population will reflect a broad cohort of patients, enhancing the generalizability of the results. The sample size and enrolment of heterogenous patients will also allow for detailed examination of the incidence, risk factors and consequences of diarrhea, and will provide the first prospective study of incident cases of ICU acquired CDAD, examining the associated illness severity in this setting.

DICE-ICU has some potential limitations. Incomplete bedside documentation of bowel movements could introduce missing data; reporting bias may influence other data collection. Given the design, observer bias might influence some practices recorded as consequences of diarrhea. Although prospective cohort studies allow for identification of risk factors, there is the potential to identify spurious associations. Infants and children are excluded from this investigation.

The DICE-ICU Study will generate current, detailed multi-center clinical evidence on a common condition affecting many critically ill patients and influencing

different healthcare professionals in the ICU setting. As an international investigation, it will also be the largest prospective study to examine the frequency of, predisposing factors for, and consequences of diarrhea to inform critical care practice and future research.

Authors' contributions: The authors' roles are as follows

Conception and design: JC Dionne, D Cook, W Alhazzani, L Mbuagbaw

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Final approval: All authors provided final approval of the manuscript

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Competing interests' statement: The authors have no competing interests to declare.

Table 1: Statistical Analysis Plan

Research objectives	**Outcome**	**Covariates**	**Analytical approach**
To determine incidence of diarrhea and consistency of bowel movements during critical illness To determine the frequency of diarrhea defined as the proportion of patients with new ICU-acquired diarrhea	**Primary Outcome** WHO-defined diarrhea **Different definitions of primary outcome** Bristol Stool Chart-defined diarrhea Bliss Stool Classification System-defined diarrhea	NA	The incidence of diarrhea will be computed as the number of new cases during ICU stay divided by the person-time at risk. Descriptive statistics (proportion of patients with diarrhea) and corresponding 95% CI
To determine risk factors associated with diarrhea during critical illness	**Primary Outcome** **Dependent variable** WHO-defined diarrhea	Age, Sex, APACHE II Score, drugs (motility modifiers, opiates, stool softeners), prior gastrointestinal disease, center	Logistic regression
SECONDARY OUTCOMES			
Research objective	**Secondary Outcome** **Dependent variable**	Covariates	Analytic approach
To determine the consequences of diarrhea	Time to ICU discharge Time to hospital discharge	WHO-defined diarrhea, Age, Sex, APACHE II Score	Cox regression
	Mortality		Logistic regression
Research objective	**Secondary Outcome**	**Covariates**	**Analytical approach**
To determine the incidence of *Clostridium difficile*-associated diarrhea (CDAD) during critical illness	IDSA-defined CDAD ESCMID-defined CDAD ACG-defined CDAD	NA	Descriptive statistics (proportion of cases with diarrhea during study period)

To determine agreement between WHO and Bristol and Bliss scores	Chance corrected agreement (Kappa score)	NA	Kappa statistic with 95% CI

Abbreviations: Acute Physiology and Chronic Health Evaluation II (APACHE II); World Health Organization (WHO), *Clostridium-difficile* Associated Diarrhea (CDAD); Confidence Intervals (CI); European Society of Clinical Microbiology and Infectious Diseases (ESCMID); Infectious Disease Society of America (IDSA); American College of Gastroenterology (ACG); Not applicable(NA)

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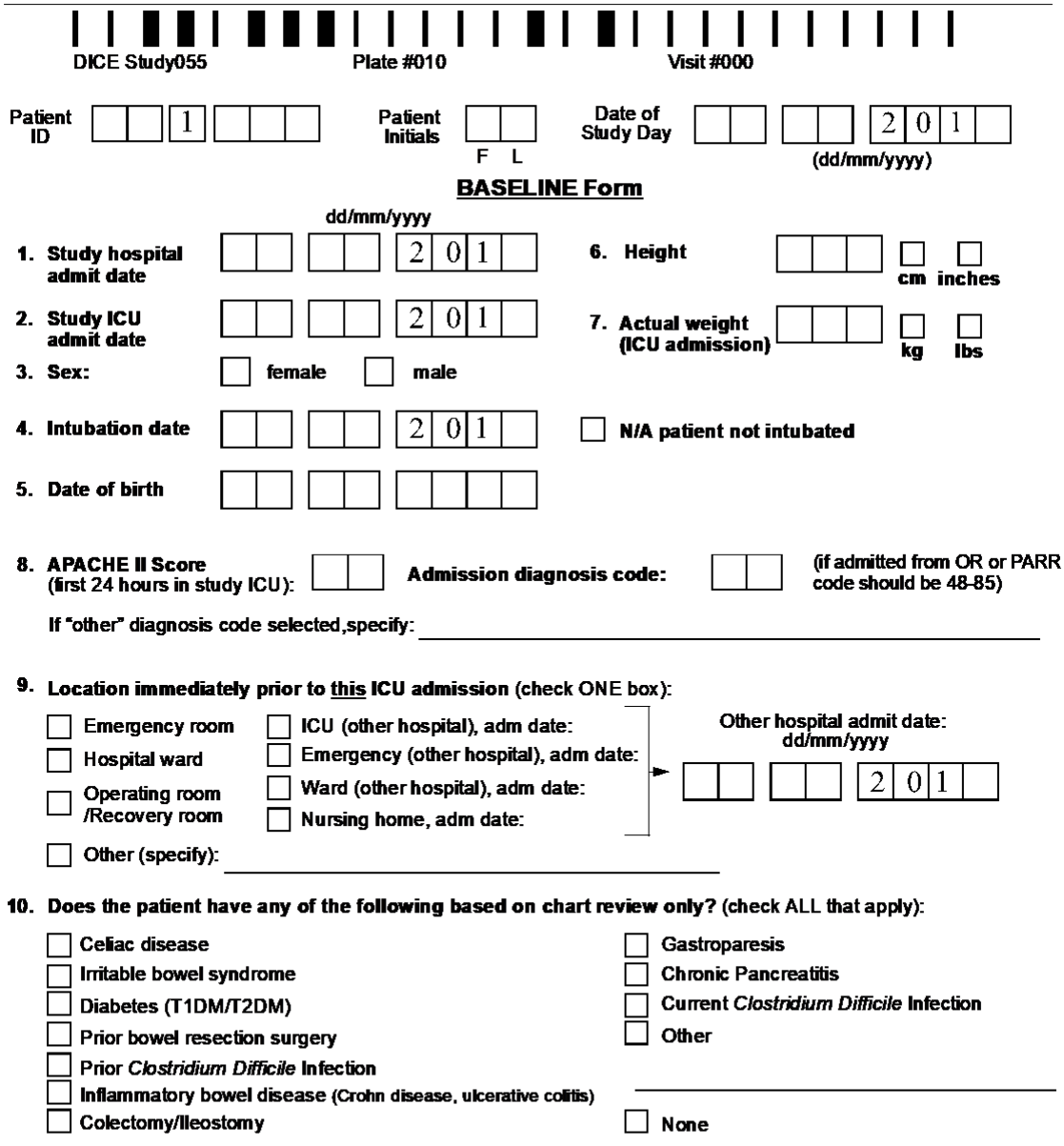
Appendix – DICE Consent Release Forms



DICE Study055 Plate #010 Visit #000

Patient ID 1 Patient Initials F L Date of Study Day 2 0 1 (dd/mm/yyyy)

BASELINE Form

dd/mm/yyyy

1. **Study hospital admit date** 2 0 1
2. **Study ICU admit date** 2 0 1
3. **Sex:** ☐ female ☐ male
4. **Intubation date** 2 0 1 ☐ **N/A patient not intubated**
5. **Date of birth**
6. **Height** ☐ cm ☐ inches
7. **Actual weight (ICU admission)** ☐ kg ☐ lbs
8. **APACHE II Score** (first 24 hours in study ICU): **Admission diagnosis code:** (if admitted from OR or PARR code should be 48-85)

If "other" diagnosis code selected,specify: _____

9. **Location immediately prior to this ICU admission** (check ONE box):

☐ Emergency room
☐ Hospital ward
☐ Operating room /Recovery room
☐ ICU (other hospital), adm date:
☐ Emergency (other hospital), adm date:
☐ Ward (other hospital), adm date:
☐ Nursing home, adm date:

Other hospital admit date: dd/mm/yyyy 2 0 1

☐ Other (specify): _____

10. **Does the patient have any of the following based on chart review only?** (check ALL that apply):

☐ Celiac disease
☐ Irritable bowel syndrome
☐ Diabetes (T1DM/T2DM)
☐ Prior bowel resection surgery
☐ Prior *Clostridium Difficile* Infection
☐ Inflammatory bowel disease (Crohn disease, ulcerative colitis)
☐ Colectomy/Ileostomy
☐ Gastroparesis
☐ Chronic Pancreatitis
☐ Current *Clostridium Difficile* Infection
☐ Other _____
☐ None

DICE Study055 Plate #020

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day (dd/mm/yyyy) 2 0 1

DAILY DATA FORM (page 1 of 4)

1. Advanced life support strategies received today

1. Invasive mechanical ventilation ☐ No ☐ Yes, if yes specify: ☐ ETT ☐ tracheostomy tube
2. Non-invasive mechanical ventilation (including CPAP/BiPAP for any duration, e.g., nocturnal) ☐ No ☐ Yes, if yes specify: ☐ CPAP ☐ BiPAP
3. Inotropes or vasopressor infusions (check all) ☐ No ☐ Yes
   - ☐ dopamine ☐ norepinephrine ☐ phenylephrine ☐ milrinone
   - ☐ dobutamine ☐ epinephrine ☐ vasopressin ☐ midodrine
4. Was dialysis performed today? ☐ No ☐ Yes, specify
   - ☐ intermittent (IHD) ☐ continuous (CRRT) ☐ peritoneal ☐ other (specify):_____

2. Is this patient enrolled in the PROSPECT Pilot or RCT? ☐ No ☐ Yes

3. Laboratory results today (from AM Blood Work)

eukocytes	. ☐ x10^9/L ☐ mm^3	Sodium	(mmol/L or mEq/L)	Albumin	. ☐ g/L ☐ g/dL
lemoglobin	. ☐ g/L ☐ g/dL	Potassium	. (mmol/L or mEq/L)	Calcium	. ☐ mmo ☐ mg/d
latelets	☐ x10^9/L ☐ mm^3	Chloride	(mmol/L or mEq/L)	Magnesium	. ☐ mmol/L ☐ mg/dL
icarb	(mmol/L or mEq/L) ☐ < or ☐ >	Creatinine	. ☐ umol/L ☐ mg/dL	Phosphate	. ☐ mmol/L ☐ mg/dL

4. Did the patient receive any nutrition today? ☐ No ☐ Yes, specify:

☐ Enteral Nutrition ☐ Trophic Feeds (defined as 10-20 mls/hr) ☐ Clear Fluids
☐ Diet as tolerated ☐ TPN ☐ Full Fluids

5. What activities were achieved today (Check ALL that apply)?

☐ Chest physio ☐ Up to chair ☐ Bike ☐ Bed exercises ☐ Ambulation ☐ None

6. Was a new antibiotic started today? ☐ No ☐ Yes

7. Was there a change in antibiotics today? ☐ No ☐ Yes

8. Were any of the following infections suspected today? ☐ N/A, infections not specified.

Respiratory Infection	☐ No	☐ Yes, was the culture positive?	☐ No	☐ Yes, spec: _____	
Blood stream infection	☐ No	☐ Yes, was the culture positive?	☐ No	☐ Yes, spec: _____	
Intra-abdominal infection	☐ No	☐ Yes, was the culture positive?	☐ No	☐ Yes, spec: _____	
Urinary tract infection	☐ No	☐ Yes, was the culture positive?	☐ No	☐ Yes, spec: _____	
C difficile associated diarrhea	☐ No	☐ Yes, was the culture positive?	☐ No	☐ Yes, spec: _____	
Stool virology	☐ No	☐ Yes, was the culture positive?	☐ No	☐ Yes, spec: _____	
Other infection (e.g., meningitis, sinusitis) Please specify: _____	☐ No	☐ Yes, was the culture positive?	☐ No	☐ Yes, spec: _____	
Other infection (e.g., meningitis, sinusitis) Please specify:	☐ No	☐ Yes, was the culture positive?	☐ No	☐ Yes, spec: _____	

DICE Study055 Plate #021 Study Day

Patient ID 1 Patient Initials F L Date of Study Day 2 0 1 (dd/mm/yyyy)

DAILY DATA FORM (page 2 of 4)

9. Did the patient receive any of the following?

1. H-2 receptor antagonist — No ☐ Yes ☐ If yes, specify: ☐ cimetidine (Tagamet) ☐ famotidine (Pepcid) ☐ other, specify: ☐ ranitidine (Zantac) ☐ nizatidine (Axid) _____ and specify: ☐ IV ☐ PO ☐ Both

2. Proton-pump inhibitor — No ☐ Yes ☐ If yes, specify ☐ lansoprazole (Prevacid) ☐ esomeprazole (Nexium) ☐ dexlansoprazole (Dexilant) ☐ omeprazole (Losec) ☐ pantoprazole (e.g., Pantoloc, Tecta) ☐ rabeprazole (Pariet) and specify: ☐ IV ☐ PO ☐ Both

3. Motility agent — No ☐ Yes ☐ If yes, specify ☐ domperidone (Motilium) ☐ metoclopramide (Maxeran) ☐ erythromycin Dose mg/24 hours ____ Dose mg/24 hours ____ Dose mg/24 hours ____ and specify ☐ other (specify) _____ Dose mg/24 hours ____ ☐ IV ☐ PO ☐ Both

4. Sorbitol/ Hyperosmolar agents — No ☐ Yes ☐ If yes, specify ☐ Metformin ☐ Phenytoin ☐ Magnesium

5. Laxative, suppository or stool softener — No ☐ Yes ☐ If yes, specify ☐ senna ☐ golytely ☐ lactulose ☐ colace ☐ citro-mag ☐ peglyte ☐ dulcolax ☐ glycerin ☐ other (specify) _____

6. Enema — No ☐ Yes ☐ If yes, specify number received and type: ____ ☐ Fleet ☐ Soap suds ☐ Lactulose ☐ Milk and Molasses

7. Opiates — No ☐ Yes ☐ If yes, please complete the **Opiate Form**

8. Neuromuscular blockers — No ☐ Yes ☐ If yes, specify ☐ rocuronium ☐ atracurium ☐ mivacurium ☐ vecuronium ☐ succinylcholine ☐ cisatracurium ☐ pancuronium

9. Probiotics — No ☐ Yes ☐ If yes, specify ☐ Bio K ☐ Other, specify: _____ ☐ Lactobacillus

10. Chemotherapy agents (secreatory diarrhea) — No ☐ Yes ☐ If yes, specify ☐ Cyclophosphamide ☐ Capecitabine ☐ Docetaxel ☐ Paclitaxel ☐ Methotrexate ☐ Cisplatin ☐ Doxorubicin ☐ Topotecan ☐ Interferon ☐ Cytosine ☐ 5-fluorouracil ☐ Lapatinib ☐ Rinotecan ☐ Daunorubicin ☐ Oxaliplatin ☐ Other, specify: _____

11. Acetaminophen — No ☐ Yes ☐ If yes, specify ☐ Suspension ☐ PO ☐ Both suspension and PO

DICE Study055 Plate #022

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day (dd/mm/yyyy) 2 0 1

DAILY DATA FORM (page 3 of 4)

10. Did the patient receive any of the following antibiotics today (Please check ALL that apply)?

1. Beta Lactams — No ☐ Yes ☐ If yes, specify

- ☐ Penicillin G
- ☐ Penicillin V
- ☐ Ampicillin
- ☐ Ampicillin-Sulbactam
- ☐ Amoxicillin
- ☐ Amoxicillin-Clavulanate
- ☐ Piperacillin/Tazobactam
- ☐ Oxacillin
- ☐ Dicloxacillin
- ☐ Flucloxacillin
- ☐ Nafcillin
- ☐ Ticarcillin/Clavulanate
- ☐ Cloxacillan
- ☐ Not specified

2. Cephalosporins — No ☐ Yes ☐ If yes, specify

- ☐ Cefazolin
- ☐ Ceflexin (oral)
- ☐ Cefadroxil
- ☐ Cefuroxime
- ☐ Cefotiam
- ☐ Cefuroxime Cefepime
- ☐ Cefaclor (oral)
- ☐ Loracarbef
- ☐ Cefoxitin
- ☐ Cefotaxime
- ☐ Ceftriaxone
- ☐ Ceftazidime
- ☐ Cefepime
- ☐ Cefixime (oral)
- ☐ Cefpodoxime
- ☐ Cefdinir
- ☐ Proxetil (oral)
- ☐ Ceftibuten (oral)
- ☐ Ceftobiprole
- ☐ Ceftaroline
- ☐ Ceftazidime/Avibactam
- ☐ Ceftolozane/Tazobactai
- ☐ Not specified

3. Carbapenems — No ☐ Yes ☐ If yes, specify

- ☐ Imiperem
- ☐ Meropenem
- ☐ Ertapenem
- ☐ Doripenem
- ☐ Not specified

4. Aminoglycosides — No ☐ Yes ☐ If yes, specify

- ☐ Streptomycin
- ☐ Gentamicin
- ☐ Tobramycin
- ☐ Netilmicin/Amikacin
- ☐ Not specified

5. Quinolones — No ☐ Yes ☐ If yes, specify

- ☐ Norfloxin
- ☐ Enoxacin
- ☐ Ofloxacin
- ☐ Ciprofloxacin
- ☐ Levofloxacin
- ☐ Moxifloxacin
- ☐ Not specified

6. Tetracyclines — No ☐ Yes ☐ If yes, specify

- ☐ Tetracycline
- ☐ Doxycycline
- ☐ Minocycline
- ☐ Tigecycline
- ☐ Not specified

7. Nitromidazoles — No ☐ Yes ☐ If yes, specify

- ☐ Metronidazole (Flagyl) → ☐ IV ☐ PO

8. Macrolides — No ☐ Yes ☐ If yes, specify

- ☐ Erythromycin
- ☐ Spiramycin
- ☐ Roxithromycin
- ☐ Clarythromycin
- ☐ Azithromycin
- ☐ Not specified

9. Lincosamides — No ☐ Yes ☐ If yes, specify

- ☐ Clindamycin

DICE Study055 Plate #023

Study Day ☐☐

Patient ID ☐☐1☐☐☐ Patient Initials ☐☐ (F L) Date of Study Day ☐☐ ☐☐ (dd/mm/yyyy) 2☐1☐

DAILY DATA FORM (page 4 of 4)

10. Did the patient receive any of the following antibiotics today (Please check ALL that apply)? CONTINUED

10. Azole Derivatives — No ☐ Yes ☐ If yes, specify
- ☐ Miconazole
- ☐ Ketoconazole
- ☐ Fluconazole
- ☐ Itraconazole
- ☐ Voriconazole
- ☐ Posaconazole
- ☐ Amphotericin
- ☐ Clotrimazole
- ☐ Isavuconazonium
- ☐ Not specified

11. Echinocandins — No ☐ Yes ☐ If yes, specify
- ☐ Caspofungin
- ☐ Anidulafungin
- ☐ Micafungin
- ☐ Not specified

12. Glycopeptide — No ☐ Yes ☐ If yes, specify
- ☐ Vancomycin → ☐ IV ☐ PO ☐ PR
- ☐ Daptomycin

13. Monobactams — No ☐ Yes ☐ If yes, specify
- ☐ Aztreonam

14. Antivirals — No ☐ Yes ☐

15. Other — No ☐ Yes ☐ If yes, specify
- ☐ Trymethoprim/Sulfamethoxazole
- ☐ Rifampin
- ☐ Rifaximin
- ☐ Nitrofurantoin (Macrobid)
- ☐ Linezolid
- ☐ Fosfomycin
- ☐ Quinupristin/Dalfopristin
- ☐ Fidaxomicin
- ☐ Chlorhexidine
- ☐ Nystatin
- ☐ Other (specify): _____

16. Last day of study daily data collection?

- ☐ No
- ☐ Yes, patient died, was discharged to the ward, or study stopped at 70 days (submit **Final Status Form**)
- ☐ Yes, consent withdrawn for further data collection (submit a **Final Status Form**)

DICE Study055 Plate #024

Study Day ☐☐

Patient ID ☐☐1☐☐☐ Patient Initials ☐☐ (F L) Date of Study Day (dd/mm/yyyy) ☐☐ ☐☐ 201☐

OPIATE & SEDATION FORM

1. Did the patient receive any of the following Opiods?

Drug	Route	Dose mg/24 hours
☐ Morphine	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Hydromorphone	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Percocet or Oxycodone	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Propofol	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Midazolam	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Diazepam	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Lorazepam	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ *Fentanyl	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐ *mcg i 24 hou
☐ Codeine (or tylenol #1,2 or 3)	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Demerol	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Methadone	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ *Dexemedetomidine	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐ *mcg i 24 hou
☐ Phenobarbitol	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Tramadol	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Other (specify): ______	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Other (specify): ______	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Other (specify): ______	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Other (specify): ______	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐
☐ Other (specify): ______	☐ Oral ☐ Bolus ☐ Infusion ☐ Subcut. ☐ Other spec. ______	☐☐☐☐☐.☐☐

DICE Study055 Plate #030

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day (dd/mm/yyyy) 2 0 1

DIETICIAN FORM

1. Please specify the diet the patient is receiving today? (check all that apply)

- ☐ Clear fluids
- ☐ Full fluids
- ☐ Diet as tolerated
- ☐ Enteral nutrition
- ☐ TPN
- ☐ Unknown
- ☐ Other, specify: _____
- ☐ Trophic feeds
- ☐ NPO

2. What is the patients enteral nutrition target (target as determined by RD in total)? ☐☐☐☐ ☐ kcal ☐ mls/hr ☐ mls/ 24 hour ☐ Not specified

3. What percentage of the patients nutritional target did they receive? ☐☐☐ % ☐ Not specified

4. Were feeds interrupted? ☐ No ☐ Yes, specify

- ☐ High residuals
- ☐ Pre-procedure
- ☐ Vomiting
- ☐ Bleeding
- ☐ Ileus
- ☐ Aspiration
- ☐ Other, specify: _____
- ☐ Unknown

5. Is the patient receiving TPN?

☐ No ☐ Yes, specify

- ☐ Inadequate absorption (short bowel syndrome)
- ☐ Bowel obstruction
- ☐ Malnutrition
- ☐ Intra-abdominal Sepsis
- ☐ Gastrointestinal fistula
- ☐ Prolonged bowel rest
- ☐ Ileus
- ☐ Other, specify: _____

and specify what formulation:

- ☐ Peripheral/central starter formula
- ☐ Peripheral/central formula
- ☐ Central formula
- ☐ Volume restricted central formula
- ☐ Custom formula

and specify flow rate: ☐ 50 ☐ 85 ☐ 100 ☐ Other, specify: _____

and specify Total 24 hour volume: ☐ 1200 ☐ 2040 ☐ 2400 ☐ Other specify: _____

and specify lipid (intralipid) ☐ 50 ☐ 60 ☐ 85 ☐ Other specify: _____

6. Is the patient receiving free water? ☐ No ☐ Yes, specify how many mls in 24 hours ☐☐☐☐

DICE Study055 Plate #031

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day (dd/mm/yyyy) 2 0 1

DIETICIAN FORM

7. Did the patient receive any enteral or oral nutrition today? ☐ No ☐ Yes, specify:

- ☐ Jevity 1.0 Cal (+ fibre)
- ☐ Jevity 1.2 Cal (+ fibre)
- ☐ Jevity 1.5 Cal (+ fibre)
- ☐ Nepro Carb Steady (1.8 kcal/mL + fibre)
- ☐ Nutren 1.5
- ☐ Peptamen 1.0
- ☐ NutriHep (1.5 kcal/mL)
- ☐ Promote (1.0 kcal/mL)
- ☐ Peptamen AF 1.2 Cal (fish-oils and prebiotics)
- ☐ Peptamen 1.5 Cal
- ☐ Isosource VHN (1.0 kcal/mL + fibre)
- ☐ Isosource VHP (1.0 kcal/mL)
- ☐ Isosource HN 1.2
- ☐ Isosource HN 1.2 (+ fibre)
- ☐ Isosource 1.5 (+ fibre)
- ☐ OXEPA (1.5 kcal/mL)
- ☐ Optimental 1.0 kcal/mL
- ☐ Glucerna 1.0 kcal/mL + fibre
- ☐ Resource 2.0
- ☐ Diabetic Resource 1.06 (+ fibre)
- ☐ TwoCal HN 2.0 (+ fibre)
- ☐ Novosource Renal 2.0
- ☐ Vital 1.0
- ☐ Replete
- ☐ Other, specify _____
- ☐ Ensure High Protein (1.0 kcal/mL)
- ☐ Ensure Plus Calories (1.5 kcal/ML)
- ☐ Oral (food) intake (volume not required)
- ☐ Oral (fluid) intake (volume not required)

24h total ml of enteral nutrition delivered ☐☐☐☐☐

☐ Not applicable patient not receiving enteral nutrition

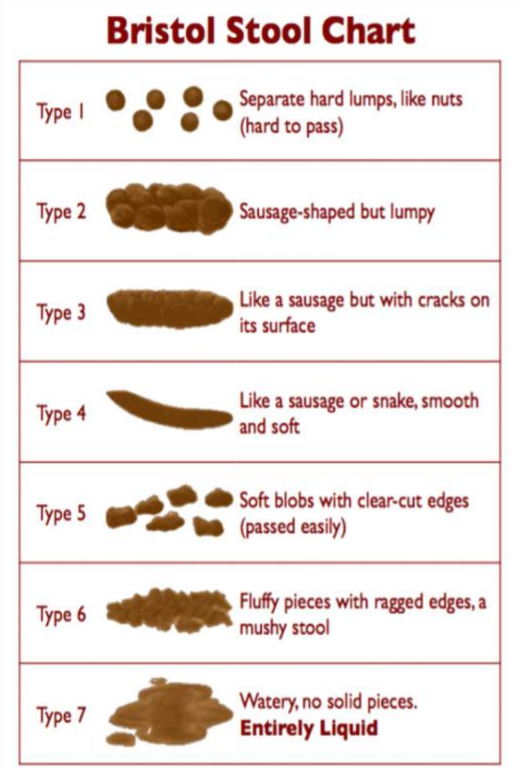
total enteral nutrition delivered ml/hr ☐☐☐☐

8. What is the feeding tube insertion site today? (check ALL that apply)

- ☐ Nasal
- ☐ Oral
- ☐ Percutaneous (specify:):
  - ☐ G tube
  - ☐ GJ tube
- ☐ Postpyloric
- ☐ No feeding tube in situ

DICE Study055

STOOL CLASSIFICATION FORM



WHO Classification of Diarrhea:

Diarrhea is defined as
the passage of 3 or more
liquid or loose stools per day

Stool Consistency Classification System (Adopted from Bliss *et al.* J. Wound Ostomy Contin. Nurs. 2001)

Hard and Formed	Soft but Formed	Loose & Unformed	Liquid
			
Having a hard or firm texture and retaining a definite shape like a banana, cigar or marbles	Retaining same general shape in the collection bag; does not spread all over the bottom of bag, or has a texture that appears like peanut butter	Lacking any shape of its own; spreads over the bottom of the collection bag; having a texture that appears like hot cereal	Like water

DICE Study055 Plate #040

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day (dd/mm/yyyy) 2 0 1

STOOL CLASSIFICATION FORM

1. **Did the patient have a bowel movement today?** ☐ No ☐ Yes, please complete question 2-7
   ☐ Page not completed
2. **Did the patient have melena or hematochezia today?** ☐ No ☐ Yes
3. **Stool Classification:**

	Bristol Type 1-7	Bliss Score	Volume			
Stool #1	☐	☐	smear ☐	medium ☐	small ☐	large ☐
Stool #2	☐	☐	smear ☐	medium ☐	small ☐	large ☐
Stool #3	☐	☐	smear ☐	medium ☐	small ☐	large ☐
Stool #4	☐	☐	smear ☐	medium ☐	small ☐	large ☐
Stool #5	☐	☐	smear ☐	medium ☐	small ☐	large ☐
Stool #6	☐	☐	smear ☐	medium ☐	small ☐	large ☐
Stool #7	☐	☐	smear ☐	medium ☐	small ☐	large ☐
Stool #8	☐	☐	smear ☐	medium ☐	small ☐	large ☐

☐ Check if more than 8 stools to be recorded for this study day (go to **Additional Stool Classification Form**)

☐ Not applicable, too watery or continuous (At least 1 stool will need to be classified above)

4. **Were there any consequences of passing of stool today?** ☐ No ☐ Yes, specify
   ☐ Feeds held ☐ Stool softener held ☐ Rectal bag applied ☐ Other, specify
   ☐ Feeds changed ☐ Prokinetic held ☐ Rectal tube inserted _____
5. **Does the patient have any of the following in place?**
   ☐ Flexiseal ☐ Ileostomy ☐ Colostomy ☐☐☐☐ Volume (mL) ☐ None
6. **Any other changes to the patient's care today that you believe contributed to a change in the patient's bowel habits?** ☐ No ☐ Yes, specify _____
7. **Did the patients bowel habits meet the WHO Classification of Diarrhea today (3 or more liquid or loose stools)?** ☐ No ☐ Yes

DICE Study055 Plate #041

Study Day

Patient 1

Patient

F L

Date of Study Day

(dd/mm/yyyy) 2011

ADDITIONAL STOOL CLASSIFICATION FORM

	Bristol Type 1-7	Bliss Score	Volume			
Stool #9			smear		medium	
			small		large	
Stool #10			smear		medium	
			small		large	
Stool #11			smear		medium	
			small		large	
Stool #12			smear		medium	
			small		large	
Stool #13			smear		medium	
			small		large	
Stool #14			smear		medium	
			small		large	
Stool #15			smear		medium	
			small		large	
Stool #16			smear		medium	
			small		large	
Stool #17			smear		medium	
			small		large	
Stool #18			smear		medium	
			small		large	
Stool #19			smear		medium	
			small		large	
Stool #20			smear		medium	
			small		large	
Stool #21			smear		medium	
			small		large	
Stool #22			smear		medium	
			small		large	
Stool #23			smear		medium	
			small		large	
Stool #24			smear		medium	

Check if more stools are to be recorded for this study day (go to **Additional Stool Classification Form**)

DICE Study055 Plate #050

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day (dd/mm/yyyy) 2 0 1

CLOSTRIDIUM DIFFICILE OUTCOME

Please submit a copy of all positive or indeterminante culture reports AND supporting clinical documentation (i.e., physician notes, nursing notes, laboratory results, radiology reports, clinical notes relating to stool, colonoscopy reports and histology reports if available)

1. ***Clostridium difficile* associated diarrhea?** ☐ No ☐ Yes, specify:

   ☐ ≥ 3 episodes of unformed stools in ≤24 hours

   AND

   ☐ *Clostridium difficile* toxin positive stool

   OR

   ☐ Colonscopic findings demonstrating pseudomembranous colitis

   OR

   ☐ Histopathological findings of pseudomembranous colitis

2. **Which test was this based upon? (Please check ALL that apply)**

   ☐ ELISA (enzyme-linked immunosorbent assay) ☐ Other, please specify: _____

   ☐ PCR (polymerase chain reaction)

   ☐ LAMP (loop-mediated isothermal amplification)

   ☐ Cell Culture Cytotoxicity Assay

3. ***Clostridium Difficile* Infection Severity (Clinical impression of Intensivist)**

   ☐ Mild ☐ Moderate ☐ Severe (e.g., toxic mega-colon)

4. **Were there any consequences of the *Clostridium difficile* infection today?**

   ☐ Toxic megacolon ☐ Septic shock ☐ Other, specify _____

   ☐ Bowel perforation ☐ Colectomy ☐ NONE

DICE Study055 Plate #060

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day (dd/mm/yyyy) 201

FINAL STATUS Form

1. **Was the patient discharged from the ICU alive?** ☐ No ☐ Yes
2. **Date of death or discharge from ICU** (dd/mm/yyyy) 201
3. **Was the patient discharged from the hospital alive?** ☐ No ☐ Yes ☐ Patient still in hospital at 1 year
4. **Date of death or discharge from hospital or if patient still hospitalized at 1 year, enter date 1 year from ICU discharge** (dd/mm/yyyy) 201
5. **Was the patient transferred to another hospital?** ☐ No ☐ Yes If yes, was it to a Long Term Care facility? ☐ No ☐ Yes

CHAPTER 3

Diarrhea During Critical Illness: A Multicenter Cohort Study (submitted to Intensive Care Medicine October 2021)

Diarrhea During Critical Illness: A Multicenter Cohort Study

Running Title: Diarrhea During Critical Illness

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Manuscript 2,998
Tables 5
Refences 32

Twitter: Diarrhea is common in ICU, rarely caused by *C. difficile,* has many management consequences, but is not associated with mortality or increased length of stay.

Key words: Diarrhea, enteral nutrition, incidence, risk factors, critical illness

Take Home: In this study we demonstrated that diarrhea is common in the ICU, and rarely was *Clostridioides difficile* the cause. Diarrhea incidence varied based on the definition applied. Diarrhea was not independently associated with mortality or increased length of stay.

Abstract

Purpose: To study the incidence, risk factors, and outcomes of diarrhea during the ICU stay.

Methods: Prospective cohort of consecutive adults in the ICU for >24 hours during a 10-week period across 12 Intensive Care Units (ICUs) internationally.

Outcomes: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 risk factors, 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 WHO definition. 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 (2.1% incidence). Independent risk factors 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 not associated with increased ICU (RR

1.06, 95% CI 0.99-1.15, p=0.108) or hospital LOS (RR 1.06, 95%CI 0.94-1.19, p=0337), or hospital mortality (RR 0.78; 95% CI 0.58-1.03, p=0.081).

Conclusion: Diarrhea is common, has several risk factors, and prompts changes in patient care, but is not associated with increased morbidity or mortality.

Introduction

The reported incidence of diarrhea during critical illness ranges from 2%-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].

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. Perhaps the most recognized stool evaluation instrument in hospitals is the Bristol Stool Chart [7], which is simple and easily applied at the bedside, comprised 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 risk factors [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 5.85,1032) 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 risk factors, and to describe the management modifications, consequences, and clinical outcomes associated with diarrhea.

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 $\geq$ 24 hours. Patients were excluded if they were in ICU for < 24 hours; 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 (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 was 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.

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 risk factors 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 testing positive subsequently during their ICU admission.

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

For all adjusted analyses, we used generalized linear models. We specified a log link, a normal distribution (to estimated adjusted risk ratios) with clustered robust standard errors to account for potential clustering within centers. Goodness of fit was assessed using Akaike information criteria (AIC). Potential diarrhea risk factors (per the WHO definition[6])were determined based on previous studies identifying antibiotics, antifungals, suppository, prokinetics, CDAD, and enteral nutrition[2, 13, 14], further refined during the DICE pilot study[20]. The following were continuous and binary covariates: baseline factors (age, sex, APACHE II score center), and exposures in the ICU (enteral nutrition, and medications [opiates, motility agents, sorbitol, acid suppressants, total number of antibiotics and the number of days on antibiotics, and chemotherapy], as a block. We also analyzed differences in diarrhea risk factors for the Bristol Stool Chart and Bliss Stool Classification (Appendix Table 1A and 1B).

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.

We also determined the association between diarrhea and ICU and hospital length of stay, and mortality, adjusting for age, sex, and APACHE II score. Adjusted risk ratios (RR), 95% confidence intervals (CI), p-values and AIC are reported. This deviates from the previously published statistical plan[19]. Odds ratios (OR) were the initial estimate of effect planned to be reported in DICE-ICU, however, following feedback from stakeholders, an adjusted risk ratio was implemented as it is more conservative estimate, and intuitive to clinicians at the bedside. Further, we accounted for potential clustering within centers by using clustered robust standard errors. Imputation methods were determined a priori in the case of significant missing data [19]. All analyses were performed using Stata (V. 16, 2019)[23].

Results

From June 2014-August 2019, 1114 patients were enrolled at 12 academic and community ICUs in Canada, the United States, Poland and Saudi Arabia (Figure 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 (8.0), and 591 (53.2%) were mechanically ventilated at baseline (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%). Minimal data were missing; thus, 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 did not differ across centers (Appendix Table 4).

The prevalence of CDAD (Appendix Figure 1) in the ICU, including pre-ICU CDAD and ICU-acquired CDAD, was 85/1109 (7.7%). However, among 99 patients tested for CDAD, only 23 were positive (CDAD incidence in the ICU of 2.1%).

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), $p< 0.001$). The WHO definition of diarrhea identifies more patients with diarrhea and is the definition used for this study.

Risk Factors for Diarrhea

Independent diarrhea risk factors (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 a decreased risk.

Risk factors for diarrhea using the Bristol Stool Chart definition were similar to the WHO definition; however, two additional risk factors 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 risk factors 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 1A and 2B).

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 2).

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 prokinetic (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 4.0,12.0) in contrast to those without diarrhea who stayed 3.0 days (IQR 2.0,4.0). Patients with diarrhea stayed in hospital 15 days (IQR 8.0,31.0) compared to those without who stayed 7.0 days (IQR 3.0,14.0), p<0.001). However, adjusting for age, sex, APACHE II score, gastrointestinal diagnoses, diabetes and center, patients with diarrhea had a similar ICU LOS (RR 1.06, 95% CI 0.99-1.15, p=0.108) and hospital LOS (RR 1.06, 95%CI 0.94-1.19, p=0.337) to others (Appendix Table 3A). Diarrhea was not independently associated with hospital mortality (RR 0.78; 95% CI 0.58-1.03, p=0.081). The association of diarrhea with duration of ICU and hospital stay and hospital mortality was similar for the Bristol and Bliss definitions (Appendix Table 3B and 3C).

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 risk factors for diarrhea included enteral nutrition, suppository use, and number of antibiotic days, while opioid use was associated with a lower risk of diarrhea. These risk factors were consistent across definitions.

Adjusted analyses found that diarrhea was not associated with hospital mortality or longer stays in the ICU and hospital.

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, and analyzed risk factors and outcomes in the ICU setting.

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 risk factors across diarrhea definitions. The attributable morbidity and mortality of diarrhea across definitions was similar. Ensuring consistent nomenclature

in practice will improve interprofessional 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 [24, 25]. Our results are consistent with a prior study suggesting 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[26] , 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[27]. 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 was 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[28], 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 similar length of stay in the ICU and in hospital compared to other patients. Patients with diarrhea did not have 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 [29]. Translational research has shown reduced microbiome diversity in respiratory and gastrointestinal samples correlates with higher disease severity and adverse outcomes [30-33].

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. 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 risk factors 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 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 interprofessional practice, to inform translational and clinical research on enteric infectious diseases, malabsorption, and gastrointestinal dysfunction. Future investigations should examine whether addressing modifiable risk factors 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 risk factors 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.

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Declarations:

Authors' contributions: The authors' roles are as follows

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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) [8 missing]	18.8 (7.98)	19.1 (7.8)	17.8 (8.5)
Type of Patient, n (%) [7 missing]			
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 (%) [7 missing]			
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: [9 missing]			
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:			
Celiac disease [1 missing]	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			
Invasive mechanical ventilation [4 missing]	591 (53.2)	455 (55.9)	136 (46.7)
Inotropes or vasopressors [6 missing]	405 (36.5)	304 (37.3)	101 (34.9)
Dialysis/renal replacement [6 missing]	79 (7.1)	59 (7.3)	20 (6.9)

Legend for Table 1: In this table we present baseline characteristics of 1,109 critically ill patients. SD=standard deviation. APACHE=Acute Physiology and Chronic Health Evaluation. Surgical patients were defined according to Canadian Critical Care Trials group definition.

Table 2: Risk Factors for Diarrhea

	WHO Incidence: 73.8% (95% CI 71.1-76.6)			
Model	**Multivariable model (full)**		**Multivariable model (reduced)**	
Covariates	**Adjusted RR (95%CI)**	**P - value**	**Adjusted RR (95%CI)**	**P -value**
Sex	0.94 (0.89 –1.00)	0.066		
Age	1.00 (1.00 –1.00)	0.101		
APACHE II score	1.00 (0.99 –1.00)	0.173		
Opiates	0.76 (0.67 - 0.86)	<0.001	0.76 (0.68-0.86)	<0.001
Chemotherapy	1.05 (0.91 - 1.20)	0.509		
Antibiotics (total #)	1.03 (1.00 - 1.05)	0.030	1.03 (1.00-1.06)	0.097
Antibiotic days	1.02 (1.01 - 1.03)	<0.001	1.02 (1.02-1.03)	<0.001
Motility Agent	1.04 (0.98 - 1.10)	0.200		
Sorbitol	1.06 (0.96 - 1.17)	0.225		
Suppository	1.13 (1.06 - 1.19)	<0.001	1.14 (1.06-1.22)	<0.001
Enteral Nutrition	1.23 (1.16 - 1.31)	<0.001	1.23 (1.16-1.31)	<0.001
Acid Suppressants	1.08 (0.94 - 1.23)	0.294		
Gastrointestinal comorbidities**	0.98 (0.93 - 1.04)	0.507		
AIC	*0.982*		*0.982*	

Legend for Table 2: In this table we present independent risk factors 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. Celiac disease, Prior bowel resection surgery, Inflammatory bowel disease (Crohn disease, ulcerative colitis), Colectomy/Ileostomy, Chronic Pancreatitis, Gastroparesis, Diabetes. AIC= Akaike Information Criterion.

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, n (%)	118 (14.4)	4 (1.4)		
Feeds held, n (%)	52 (6.4)	0 (0)		
Feeds changed, n (%)	42 (5.1)	0 (0)		
Prokinetic held, n (%)	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, n (%)	94 (11.5)	6 (2.1)		
Other consequence, n (%)	63 (7.7)	4 (1.4)		
Rectal tube inserted, n (%)	37 (4.5)	4 (1.4)		
Rectal bag applied, n (%)	17 (2.1)	2 (0.7)		

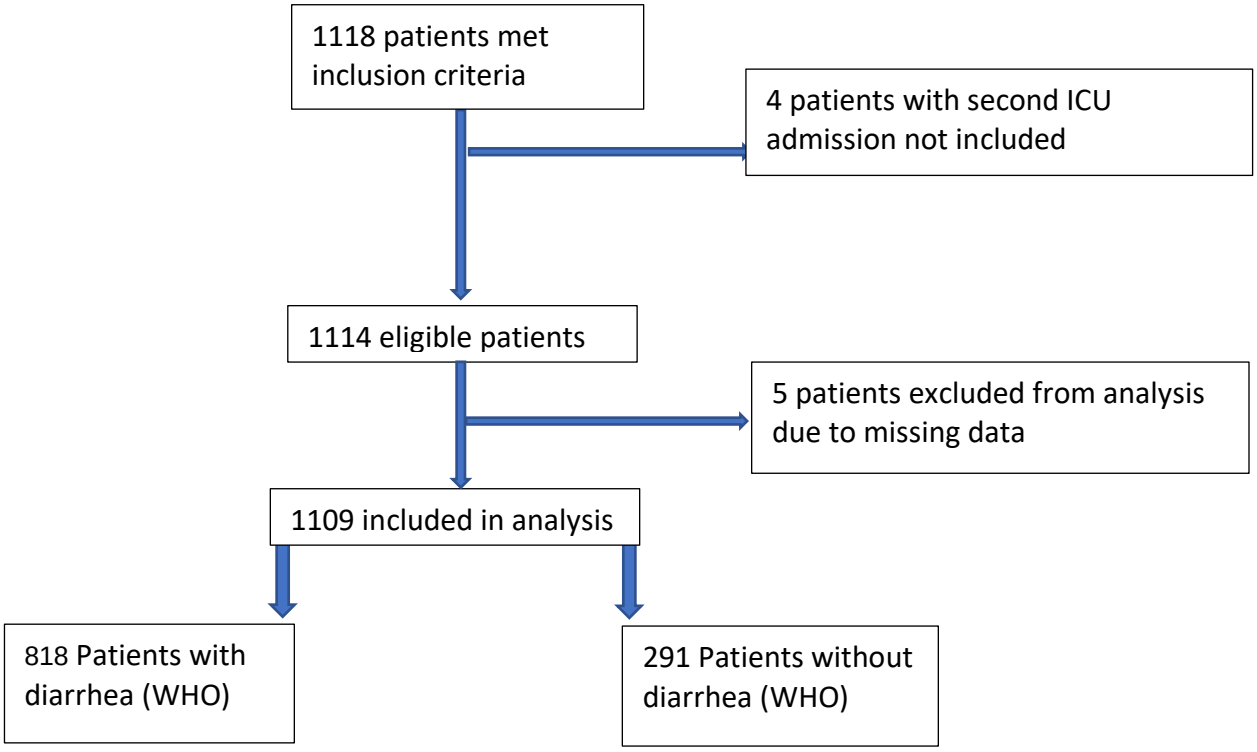
Legend for Table 3: In this table we present the management modifications and consequences of diarrhea (WHO definition) on individual management consequences. RR=Risk Ratio. *Adjusted for age, sex, APACHE II score, center.

Table 4: ICU and Hospital Length of Stay and Mortality

Variable	Death		ICU stay		Hospital stay	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Diarrhea	0.78 (0.58 - 1.03)	0.081	1.06 (0.99 - 1.15)	0.108	1.06 (0.94 - 1.19)	0.337
Sex	1.01 (0.82 - 1.24)	0.932	1.00(0.96 - 1.05)	0.854	0.99 (0.93 - 1.05)	0.755
Age	1.02 (1.01 - 1.04)	0.002	1.00 (1.00 – 1.00)	0.231	1 (0.99 – 1.00)	0.004
APACHE II score	1.04 (1.02 - 1.06)	<0.001	0.99 (0.98 - 0.99)	<0.001	0.98 (0.98 - 0.99)	<0.001

Legend for Table 4: In this table we present the association of diarrhea (WHO) on any management consequences, ICU and hospital length of stay, and mortality. The models were adjusted for age, sex, APACHE II score, center. RR=Risk Ratios, adjusted. CI=confidence interval. APACHE=Acute Physiology and Chronic Health Evaluation.

Figure 1: Flow Diagram for DICE-ICU Study



Legend for Figure 1: Flow diagram of patients enrolled in the DICE-ICU Study.

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Appendix

Table 1: Diarrhea risk factors based on the Bristol Stool Chart and Bliss Classification

Table 1A: Multivariable models for Diarrhea (Bristol Stool Chart definition) (RR)

	Bristol incidence: 53.5% (95% CI 50.4-56.4)			
Model	**Multivariable Model Bristol**		**Multivariable Model Bristol**	
Covariates	**Adjusted OR (95% CI)**	**P -value**	**Adjusted RR (95%CI)**	**P -value**
Sex	1.13 (1.00 - 1.29)	0.053	1.03 (0.98 - 1.08)	0.268
Age	1.01 (1.00 - 1.02)	0.062	1.00 (1.00 - 1.01)	0.034
APACHE II score	1.02 (0.99 - 1.05)	0.214	1.00 (1.00 - 1.01)	0.276
Opiates	0.58 (0.3 - 1.13)	0.111	0.84 (0.65 - 1.08)	0.167
Chemotherapy	1.24 (0.56 - 2.72)	0.598	1.06 (0.86 - 1.32)	0.567
Antibiotics (total #)	1.24 (0.95 - 1.62)	0.115	1.05 (1.01 - 1.1)	0.019
Antibiotic days	1.19 (1.03 - 1.37)	0.016	1.03 (1.02 - 1.04)	<0.001
Motility Agent	0.9 (0.68 - 1.18)	0.432	0.96 (0.89 - 1.04)	0.347
Sorbitol	1.71 (1.00 - 2.94)	0.051	1.2 (0.98 - 1.46)	0.078
Suppository	1.37 (0.98 - 1.92)	0.065	1.14 (1.02 - 1.27)	0.023
Enteral Nutrition	1.75 (1.19 - 2.57)	0.004	1.30 (1.13 - 1.5)	<0.001
Acid Suppressants	1.39 (0.76 - 2.54)	0.285	1.16 (0.88 - 1.52)	0.287
Gastrointestinal comorbidities**	1.49 (0.89 - 2.48)	0.130	1.11 (0.93 - 1.33)	0.236
AIC	1.202		*1.290*	

*Models adjusted for centre; ** Celiac disease, Prior bowel resection surgery, Inflammatory bowel disease (Crohn disease, ulcerative colitis), Colectomy/Ileostomy, Chronic Pancreatitis, Gastroparesis. AIC= Akaike Information Criterion.

Table 1B: Multivariable models for Diarrhea (Bliss Stool Classification System) (RR)

	Bliss incidence: 37.7% (95% CI 34.8-40.6)			
Model	**Multivariate Model Bliss**		**Multivariate Model Bliss**	
Covariates	**Adjusted OR (95% CI)**	**P -value**	**Adjusted RR (95%CI)**	**P -value**
Sex	1.35 (1.01 - 1.8)	0.043	1.11 (1.01 - 1.22)	0.030
Age	1.01 (1.00 - 1.02)	0.141	1.00(1.00 - 1.01)	0.050
APACHE II score	1.02 (0.99 - 1.04)	0.178	1.00 (0.99 - 1.01)	0.429
Opiates	0.93 (0.59 - 1.46)	0.753	1.02 (0.74 - 1.42)	0.886
Chemotherapy	1.49 (0.64 - 3.45)	0.351	1.25 (0.96 - 1.62)	0.101
Antibiotics (total #)	1.15 (0.92 - 1.44)	0.218	1.06 (1.01 - 1.12)	0.019
Antibiotic days	1.11 (1.01 - 1.22)	0.023	1.02 (1.01 - 1.03)	<0.001
Motility Agent	1.13 (0.84 - 1.5)	0.425	1.04 (0.91 - 1.18)	0.576
Sorbitol	1.64 (0.9 - 2.97)	0.105	1.32 (0.95 - 1.83)	0.097
Suppository	1.29 (0.9 - 1.85)	0.168	1.14 (0.95 - 1.35)	0.150
Enteral Nutrition	2.2 (1.5 - 3.24)	<0.001	1.67 (1.38 - 2.01)	<0.001
Acid Suppressants	2.17 (1.44 - 3.28)	<0.001	1.66 (1.15 - 2.4)	0.007
Gastrointestinal comorbidities**	1.51 (0.92 - 2.48)	0.102	1.12 (0.93 - 1.35)	0.235
AIC	1.206		1.267	

*Models adjusted for centre; ** Celiac disease, Prior bowel resection surgery, Inflammatory bowel disease (Crohn disease, ulcerative colitis), Colectomy/Ileostomy, Chronic Pancreatitis, Gastroparesis. AIC= Akaike Information Criterion.

Figure 1: CDAD DICE-ICU Incidence and Prevalence

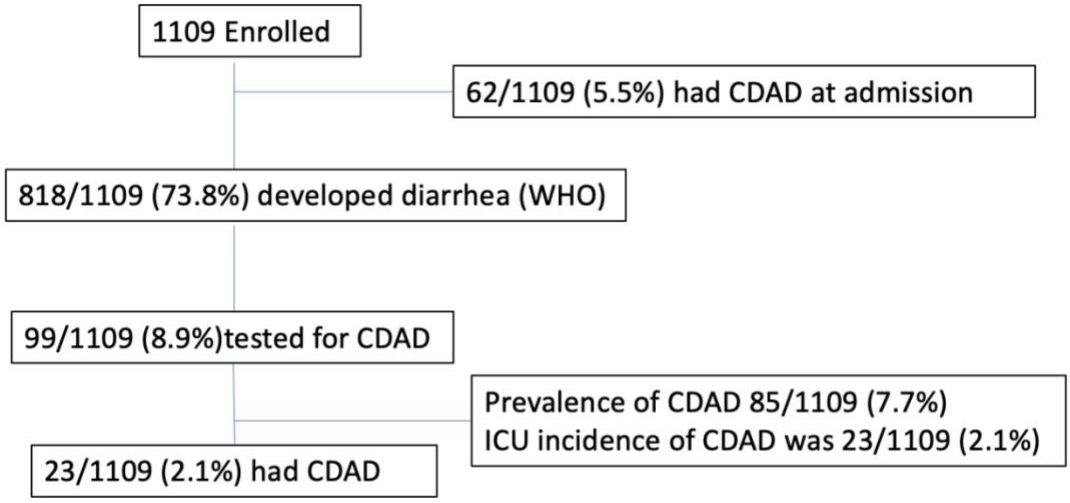


Table 2: Enteral Nutrition Components Associated with Diarrhea (WHO Definition)

	WHO Incidence: 73.8% (95% CI 71.1-76.6)	
Model	**Multivariable model (full)***	
Covariates	**Adjusted RR (95%CI)**	**P -value**
Sex	0.95 (0.90 - 1.01)	0.083
Age	1.00 (1.00 – 1.00)	0.630
APACHE II score	1.00 (1.00 – 1.00)	0.786
Opiates	0.78 (0.69 - 0.89)	<0.001
Chemotherapy	1.00 (0.87 - 1.15)	0.994
Antibiotics (total #)	1.03 (1.01 - 1.06)	0.003
Antibiotic days	1.03 (1.02 - 1.04)	<0.001
Motility Agent	1.04 (0.99 - 1.11)	0.142
Sorbitol	1.04 (0.97 - 1.12)	0.289
Suppository	1.13 (1.06 - 1.20)	<0.001
High protein	0.97 (0.93 - 1.02)	0.308
High osmolarity	1.14 (1.08 - 1.20)	<0.001
High fibre	1.11 (1.05 - 1.17)	<0.001
Acid Suppressants	1.08 (0.95 - 1.22)	0.258
Gastrointestinal comorbidities**	1.12 (1.03 - 1.22)	0.010
AIC	*0.981*	

*Model adjusted for centre; ** Celiac disease, Prior bowel resection surgery, Inflammatory bowel disease (Crohn disease, ulcerative colitis), Colectomy/Ileostomy, Chronic Pancreatitis, Gastroparesis. AIC= Akaike Information Criterion.

Table 3: Consequences of Diarrhea

Table 3A: Consequences of Diarrhea (WHO Definition)

Variable	Death		ICU stay		Hospital stay	
	RR (95% CI)	**P**	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**
Diarrhea	0.78 (0.58 - 1.03)	0.081	1.06 (0.99 - 1.15)	0.108	1.06 (0.94 - 1.19)	0.337
Sex	1.01 (0.82 - 1.24)	0.932	1.00(0.96 - 1.05)	0.854	0.99 (0.93 - 1.05)	0.755
Age	1.02 (1.01 - 1.04)	0.002	1.00 (1.00 – 1.00)	0.231	1.00 (0.99 – 1.00)	0.004
APACHE II score	1.04 (1.02 - 1.06)	<0.001	0.99 (0.98 - 0.99)	<0.001	0.98 (0.98 - 0.99)	<0.001
AIC*	1.018		0.724		1.032	

AIC= Akaike Information Criterion.

Table 3B: Consequences of Diarrhea (Bristol Stool Chart)

Variable	Death		ICU stay		Hospital stay	
	RR (95% CI)	**P**	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**
Diarrhea	0.91 (0.67 - 1.24)	0.567	1.04 (0.96 - 1.13)	0.379	1.03 (0.92 - 1.14)	0.637
Sex	1.02 (0.83 - 1.26)	0.849	1.00 (0.96 - 1.05)	0.997	0.99 (0.93 - 1.05)	0.678
Age	1.02 (1.01 - 1.04)	0.002	1.00 (1.00 – 1.00)	0.230	1.00 (0.99 – 1.00)	0.005
APACHE II score	1.04 (1.02 - 1.06)	<0.001	0.98 (0.98 - 0.99)	<0.001	0.98 (0.98 - 0.99)	<0.001
AIC*	1.024		0.726		1.034	

AIC= Akaike Information Criterion.

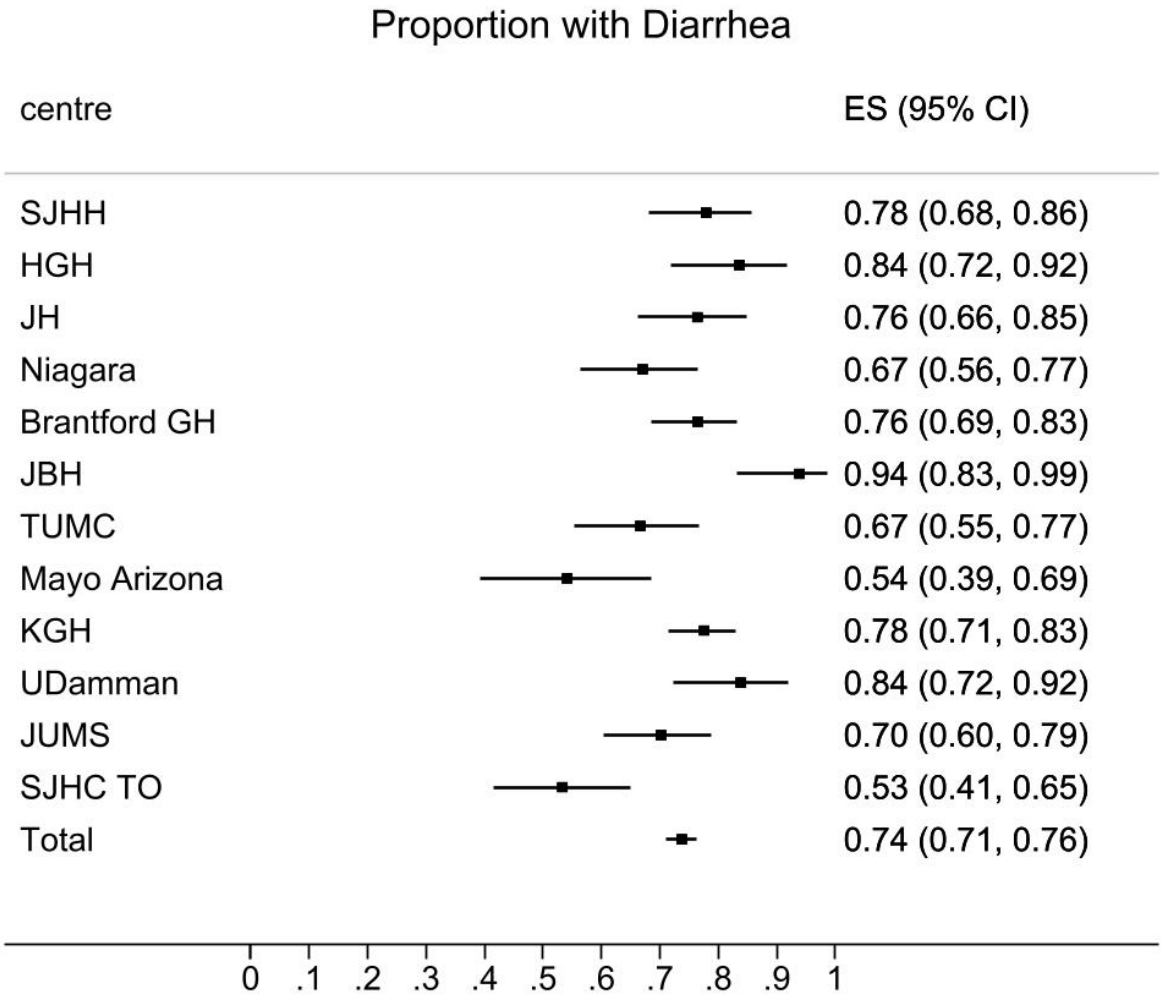
Table 3C: Consequences of Diarrhea (Bliss Stool Classification System)

Variable	Death		ICU stay		Hospital stay	
	RR (95% CI)	**P**	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**
Diarrhea	1.10 (0.82 - 1.49)	0.518	1.03 (0.95 - 1.11)	0.466	1.00 (0.90 - 1.10)	0.939
Sex	1.02 (0.82 - 1.26)	0.888	1.00 (0.96 - 1.05)	0.985	0.99 (0.93 - 1.05)	0.686
Age	1.02 (1.01 - 1.04)	0.001	1.00 (1.00 – 1.00)	0.244	1.00 (0.99 – 1.00)	0.005

APACHE II score	1.04 (1.02 - 1.06)	<0.001	0.98 (0.98 - 0.99)	<0.001	0.98 (0.98 - 0.99)	<0.001
AIC*	1.024		0.727		1.034	

AIC= Akaike Information Criterion.

Table 4: Center various in diarrhea incidence



CHAPTER 4

Content Analysis of Bowel Management Protocols For the Management of Constipation in Adult Critically Ill Patients (Published in Journal of Critical Care 58(2020) 98-104)

Content Analysis of Bowel Management Protocols For The Management of Constipation in Adult Critically Ill Patients

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Key Words: gastrointestinal, diarrhea, bowels, critical care

Conflict of Interest: None declared

Reprints: Not available

Abstract:

Objective: Alterations in bowel habits are common in the intensive care unit (ICU), and bowel protocols are gaining acceptance. Our objective was to characterize the content of bowel protocols in a cross-sectional analysis of ICUs.

Design: We engaged 44 adult ICUs to perform a content analysis of available bowel protocols, addressing 1) initiation criteria, 2) medications incorporated, 3) medication escalation, 4) discontinuation criteria, 5) stool assessment methods and 6) bowel protocol contraindications.

Setting: ICUs in Canada, the United States and Saudi Arabia

Patients: Adult patients admitted to medical and surgical ICUs in academic or community centers participating in a probiotics trial.

Interventions: None.

Measurement and Main Results: Bowel protocols were operant in 33 of 44 ICUs (79.5%). The most common medications were senna (81.0%) and bisacodyl (75.6%). Less common agents were sodium phosphate (45.9%) glycerin (43.2%), docusate sodium (43.2%), polyethylene glycol 3350 (37.8%), lactulose (29.7%), sodium citrate (16.2%), milk of magnesia (13.5%) and mineral oil (16.2%). Bowel protocols were activated by nurses (62.8%) based on initiation criteria; including no bowel movement for 24-96 hours (35.1%); opioid use (18.9%); “at risk for constipation” (13.5%); stool on digital rectal exam (10.8%); feeding initiation (10.8%); and ICU admission (8.1%). Criteria for laxative escalation included time from last bowel movement (59.4%), opioid use (18.9%), and no stool on digital rectal exam (10.8%), while 15 (40.5%) bowel protocols included diarrhea as a discontinuation criterion.

Conclusions: Bowel protocols have variable initiation, escalation, and discontinuation criteria incorporating different classes of laxatives, reflecting unclear evidence about optimal bowel management strategies in the ICU.

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Supplemental Appendix Table: 1

Introduction

Alterations in bowel habits is common in the intensive care unit (ICU). The literature regarding gastrointestinal dysfunction in the ICU is growing, however the evidence is not as robust compared to other research disciplines in critical care such as sepsis, acute respiratory distress syndrome and cardiopulmonary research. In the areas of gastrointestinal dysfunction, the interest in optimizing the treatment of constipation, diarrhea and prophylactic laxative bowel management is growing however, more research is needed. A previously conducted survey identified clinicians working the ICU felt dissatisfied to very dissatisfied with the bowel management programs at their centers and felt this is a neglected area of critical care (Knowles, 2010).

Bowel management protocols have been used to treat and prevent constipation as well as prophylactically to treat non-defecation (Hay 2019). The challenge remains in the balance of treating or preventing constipation can result in the development of diarrhea. In observational studies, constipation has been associated with increased length of hospital stay, delirium, feeding intolerance as well as increased duration of mechanical ventilation and longer length of hospital stay [3]. In Contrast, diarrhea in critically ill patients can be associated with feeding intolerance or modification of enteral nutrition, electrolyte disturbances, renal failure and skin breakdown [4]. Diarrhea can result in unnecessary testing for *Clostridioides difficile*, isolation and other interventions (e.g., insertion of fecal management devices). (Dionne 2016; Hay 2019).

Hay and colleagues (2019) conducted a meta-analysis and systematic review exploring the epidemiology of constipation and diarrhea in the ICU and the impact of prophylactic laxative bowel regimens on patient outcomes. Diarrhea and constipation

found to be common with variability and definitions applied (Hay 2019). Prophylactic bowel regimens were found to reduce constipation, may increase the risk of diarrhea, but did not impact patient important outcomes (Hay 2019). The review found similar studies to the previously published systematic review by Oczkowski et al (2017) exploring the impact of bowel protocols on feeding intolerance, constipation, and duration of mechanical ventilation reported variable results. The use of bowel protocols likely reduces the risk of constipation (relative risk [RR] 0.50, 95% confidence interval (CI) 0.25 to 1.01), although having little impact on duration of mechanical ventilation (mean difference 0.01 days, 95% CI -2.67 to 2.69) or feeding tolerance (RR 0.94, 95% CI 0.62 to 1.42) [1]. A key message of these two systematic reviews is the general dearth of research on bowel protocols in critically ill patients with respect to patient important outcomes and different mechanisms of laxative use (Hay 2019; Oczkowski, 2017). The gap in the current body of research is what bowel protocol strategies are being implemented at the bedside in ICUs.

The primary objective of this study was to characterize the content of bowel protocols for the prevention of constipation implemented in ICUs in centers that participated in a randomized trial examining the effects of probiotics for critically ill patients to prevent ICU-acquired infections [Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial (PROSPECT) NCT02462590]. Our secondary objective was to characterize: 1) initiation criteria; 2) medications incorporated; 3) approaches to protocol escalation; 4) discontinuation criteria; 5) stool assessment methods; and 6) contraindications.

Materials and Methods

This observational study was nested within the PROSPECT trial that allocated patients to receive *Lactobacillus rhamnosus* GG (Culturelle, Locin Industries Ltd) or identical placebo, administered enterally twice daily for up to 60 days while in the ICU [5]. The primary outcome of the trial was ventilator-associated pneumonia and secondary outcomes included other nosocomial infections and diarrhea. The management of diarrhea and constipation was at the discretion of the treating team. The existence of a bowel protocol was not a criterion for a center's participation in the trial.

We asked the 44 PROSPECT participating centers in Canada, the United States, Saudi Arabia, (as listed in supplement Table 1) to complete a site status form indicating whether they had a bowel protocol; if they did, our research project manager requested a copy. Bowel protocols were defined as any document that was explicitly initiated to promote bowel movements in critically ill patients. They could be stand alone documents or incorporated into the admission order set as a supplemental treatment plan. Protocols that pertained only to the care of fecal management devices were excluded.

We used content analysis and descriptive statistics (frequency and percentages) to characterize the content of existing bowel protocols. Content analysis is a research method using qualitative and/or quantitative analysis of documents to describe a phenomenon of interest [6], as used commonly in the fields of nursing, psychiatry, geriatrics, and public health [6]. The domains of interest for the classification schema were established by discussion between two investigators (JCD and DJC) and informed

by review of the bowel protocols collated; thereafter, content was abstracted by one investigator (JCD). We did not contact participating centers to document the year that the bowel protocol was developed, the frequency and focus of any updates, or the professional background of the developers. We analyzed the bowel protocols for: 1) initiation criteria, 2) medications incorporated, 3) medication escalation approaches, 4) discontinuation criteria, 5) stool assessment methods and 6) contraindications to bowel protocols.

Ethics

The PROSPECT trial received ethics approval at the Hamilton Integrated Research Ethics Board and all participating centers.

Results

All 44 ICUs responded regarding the presence or absence of a bowel protocol (100% response rate); 33 (79.5%) had at least one bowel protocol, accounting for a total of 37 bowel protocols. Of the 33 ICUs that had bowel protocols, 7 were community hospitals and 26 were academic hospitals. Of these 37 protocols, 22 protocols (59.4%) were stand-alone documents, and the remaining 15 protocols (40.5%) were embedded into ICU admission orders. Six ICUs across 5 hospitals had separate protocols for spinal cord injury patients, 4 ICUs had protocols for patients receiving opioids, and 3 sites had different protocols for surgical, cardiac and medical ICUs. Two protocols were excluded from 2 centers because they only focused on the use of fecal management devices. The 11 hospitals that did not have a specific bowel protocol were academic ICUs in Canada and the United States.

Figure 1 summarizes the laxatives used in the 37 bowel protocols. Stimulant and osmotic drug classes were the most commonly utilized in the protocols reviewed. The most commonly used stimulant laxatives included senna (n=30, 81.0%) and bisacodyl (n=28, 75.6%). Other laxatives were sodium phosphate (n=17, 45.9%), glycerin (n=16, 43.2%), docusate sodium (n=16, 43.2%), polyethylene glycol (PEG)-3350 (n=14, 37.8%), lactulose (n=11, 29.7%) and sodium citrate (n=6, 16.2%). Mineral oil (n=3, 8.1%) and milk of magnesia (n=5, 13.5%) were less often incorporated. Route of administration of laxatives included oral, suppository and enema delivery. Of the 10 different laxatives identified in the protocols, the dosage range varied widely. None of the bowel protocols included recommendations for use of prokinetics or provided explicit guidance in terms of daily maintenance therapy to prevent constipation (e.g., daily dosing of PEG-3350 to prevent constipation). Other than enteral nutrition being an initiation criterion, none of the bowel protocols recommended the addition of fiber to feeds to treat constipation or incorporated strategies to minimizing opioids. Only one bowel protocol indicated the need for an abdominal x-ray if no bowel movement occurred after use of laxative therapy.

The decision to activate a bowel protocol was typically driven by the bedside nurse (n=23, 62.8%) based on initiation criteria outlined in the protocol ordered by a physician. These criteria included: 1) no bowel movement for 24-96 hours (n=13, 35.1%; 1 protocol had a 24-hour criterion,7 protocols used 48 hours, 3 protocols used at least 72 hours and 2 protocols had greater than 96 hours as a criterion); 2) opioid use (n=7, 18.9%); 3) “at risk for constipation” without definition (n=5, 13.5;%); 4) stool on digital rectal exam performed by nurses (n=4, 10.8;%); 5) enteral nutrition initiation (n=4,

10.8%); and 6) ICU admission (n=3, 8.1%). The remaining protocols had no explicit initiation criteria (Figure 2).

Criteria for laxative escalation included time from last bowel movement (n=22, 59.4%); opioid use (n=7, 18.9%); or no stool on digital rectal exam (n=6, 16.2%). Escalation strategies included increasing the frequency of a laxative, combination therapy with other medications, and/or the addition of enema therapy or additional oral therapy. The remaining protocols did not specify when to change drug dose or class. Fifteen (40.5%) bowel protocols included diarrhea as a discontinuation criterion (Table 1). The protocols that did not have an initiation criterion, could still be escalated by the bedside nurse as there were set orders for laxatives on an “as-needed basis”. Only 2 protocols incorporated stool assessment charts to descriptively track bowel movements; these included the use of the Bristol Stool chart and a site-specific definition. While this analysis was not focused on the use of or fecal management devices, rectal tubes were incorporated into a possible definition of diarrhea (e.g., >500mls of stool via rectal tube) at one center.

Contraindications to the use of bowel protocols (Table 2) were present in 15 (40.5%) protocols and included: 1) renal disease (n=8, 21.6%;specifically use of sodium phosphate enemas); 2) major abdominal surgery or bowel obstruction (n=8, 21.6%); 3) neutropenia or bone marrow transplant (n=5, 13.5%); 4) nausea, vomiting or undiagnosed abdominal pain (n=4, 10.8%); 5) platelet count < 50 x 10^9/L. (n=2, 5.2%); and 6) fecal impaction (n=1, 2.7%).

Discussion

In this study, most ICUs participating in the PROSPECT trial reported having a bowel protocol at their institution. These protocols were highly variable in their constitution with differing criteria for initiation, medications used, contraindications to ongoing usage as well as their escalation. Very few bowel protocols had discontinuation criteria, which is important to minimize the risk of iatrogenic diarrhea. Only two protocols were guided by a stool assessment chart, which can objectively and consistently characterize and track bowel movements [7]. The lack of explicit tracking of bowel movements in response to use of a bowel protocol may relate to the fact that no specific stool chart had been validated in the critical care setting until just recently [8]. Although, not previously validated, the Bristol Stool Chart has been used in the ICU research setting for the study of diarrhea in 44 patients (Bishop, 2010).

The findings of this study demonstrate that time of the last bowel movement was most commonly used as a bowel protocol initiation or escalation criterion. However, protocols lacked maintenance therapy (e.g., daily dosing of laxative therapy to maintain regularity of bowel movements). Timely initiation of bowel protocols is challenging in critically ill adults due to lack of evidence about patients' pre-existing “normal” bowel habits, and generally unclear optimal or “personalized” initiation criteria. Bowel protocols for the prevention and treatment of constipation, prophylactic laxatives in non defecation, prevention of opioid induced constipation, will likely require different initiation criteria laxative classes, doses and will have different outcomes. For example, a prophylactic bowel protocol may decrease constipation in this population when initiated early. In an observational study [9], early initiation of prophylactic PEG-4000 was

associated with less gastrointestinal paralysis compared to its initiation following 4 days without a bowel movement.

The bowel protocols analyzed in this study incorporated a variety of medications - most commonly stimulant laxatives such as senna. Surprisingly, many protocols did not include medications studied in previous randomized control trials of bowel protocols such as lactulose and PEG [1]. Different regimens of such medications include: 1) lactulose administered every 8 hours compared to usual care [10]; 2) lactulose administered every 12 hours compared to usual care [10]; 3) lactulose and PEG administered every 8 hours versus placebo (including rescue therapy with enemas and intravenous neostigmine if patients enrolled in the treatment arm had not had a bowel movement for 7 days after being treated with PEG) [11]; and 4) lactulose administered 4 times daily compared to placebo [12]. In the context of limited evidence, the development of future ICU bowel protocols should include lactulose and PEG, as these drugs appear to be the primary laxatives employed.

A recent single centre pilot cluster cross-over RCT (Hay 2019) that study three regimens: 1) docusate sodium with senna tables BID when feeding was initiated. If no bowel movement by day 5 an osmotic laxative was added (movicol sachet) administered daily, 2) No laxatives administered, until day 3 after feeding initiation at which point docusate sodium, senna and 20 mls of lactulose were administer twice a day and 3) no laxative administration until after 6 days of feeding, when patient was administered docusate sodium, senna and 20 mls of lactulose twice a day (Hay 2019). The primary outcome was insertion of a rectal tube for diarrhea. Secondary and tertiary outcomes included diarrhea, ileus, obstruction, skin breakdown, duration of mechanical

ventilation, ICU length of stay, and 30-day mortality (Hay 2019). A total of 570 patients were enrolled across all regimens. A total of 53/570 (9.3%) patients required a rectal tube, 78/570 (13.7%) developed diarrhea, 13/570 (2.3%) developed ileus or obstruction, *Clostridioides Difficile* occurred in 1 patient. However, 18/570 (3.2%) developed local pressure ulcers. In terms of terirary outcomes, duration of mechanical ventilation was 81.4 hours (39.0-156.0), ICU length of stay 4.9 days (3.0-8.0) and 30-day mortality 108/570 (18.9%) (Hay 2019). The authors found that withholding laxatives until day 6 of feeding did not result in an increase rate of complications (Hay 2019). More research is needed to examine which regimens and dosages are the most effective for incorporating into protocols, as well as which initiation and escalation criteria are most appropriate. In the bowel protocols we examined, concomitant feeding formulae were not well described. Further research is required to identify the impact of enteral nutrition and the addition of fiber to feeds to prevent constipation and diarrhea, so as to inform synergistic strategies to manage gut motility.

It is important to highlight that respect to prophylactic laxative bowel protocols, that there is no evidence that non-defecation needs to be prevented. It is important that future studies not only examined the reason for the bowel protocols (i.e. opioid use, constipation, prophylactic) but should address which regimens and medication should be used, incorporate stool assessment charts, and incorporate nutrition alterations (i.e. addition of fiber, change in rate and location of feeding administration. It is also vital that future research assesses how these protocols are implemented and if these protocols improve patient outcomes compared to a control (Hay, 2019; Hay 2019).

Strengths of this study include the identification of all contemporary ICU-specific bowel protocols and their detailed characterization using document analysis. We characterized 6 dimensions of 37 bowel protocols in centers caring for heterogeneous critically ill patients. These protocols represent tools available for diverse practice settings including both academic and community centers participating in the PROSPECT trial from different countries.

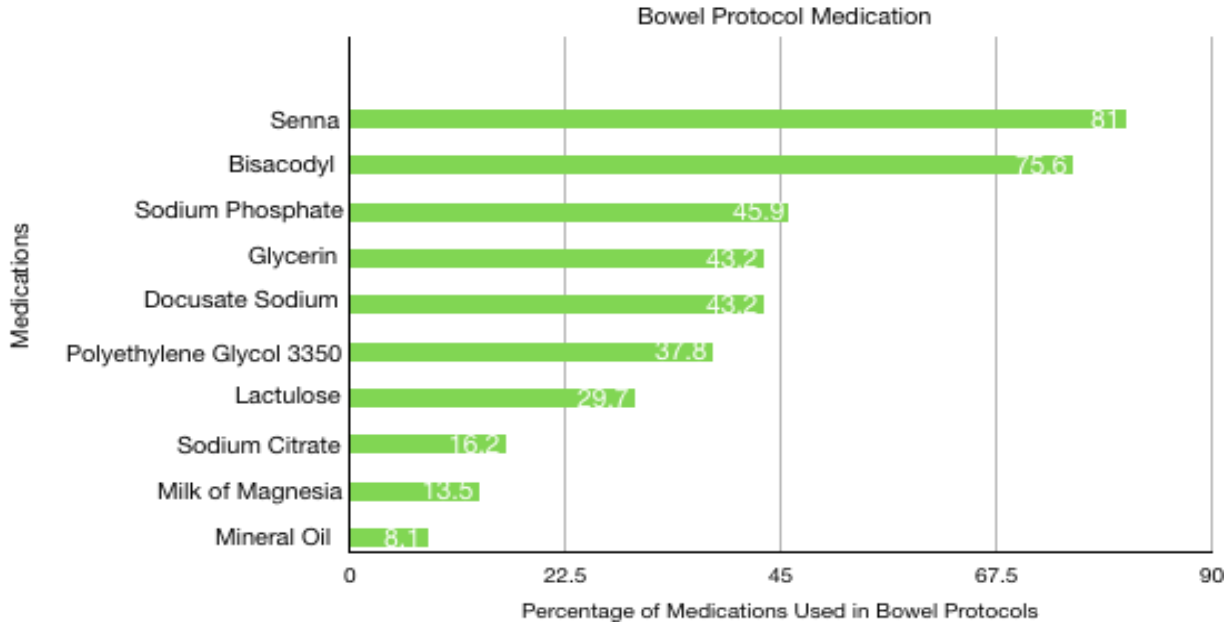
Our study has several limitations. We did not critically appraise the evidence behind each component of these protocols, which is in general limited, nor did we collect stool management methods encoded in electronic medical records or bowel protocol utilization profiles. We did not survey institutions which did not have a bowel protocol to inquire about why not. We did not examine how these bowel protocols were developed, implemented at the bedside or measure compliance. Another limitation is the confounding that was inherent into the treatment goals for the bowel protocol implementation including prevention of constipation, treatment of constipation and opioid use and its effect on gut motility. Finally, selection bias may have been introduced by the convenience sample of centers participating in the PROSPECT trial, although these hospitals reflect a diverse group of ICUs.

Future bowel protocols should incorporate explicit definitions of constipation and diarrhea in this patient population, in addition to the utilization of stool tracking tools.

Conclusion

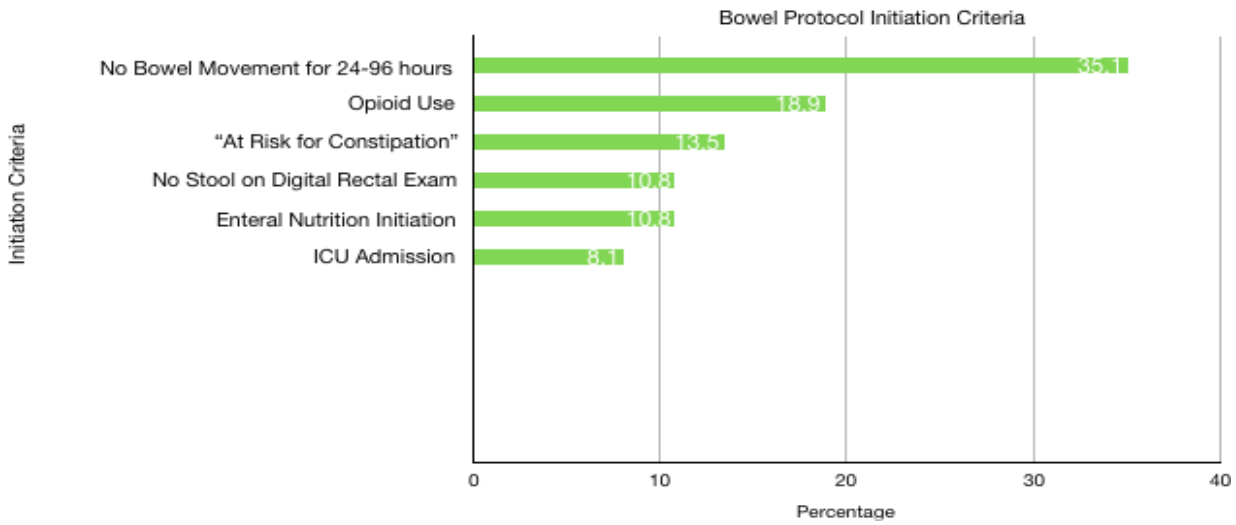
In summary, we found that bowel protocols have variable and sometimes unspecified initiation criteria, unclear escalation and discontinuation criteria. Uncertainty about optimal bowel management strategies is reflected in these protocols, underscoring how more research is needed in this often-neglected domain of practice. Further investigations focusing on the class and dose of effective strategies for critically ill patients is needed.

Figure 1: Bowel Protocol Medications



Legend for Figure 1: Medications included in all bowel protocols are shown in this table. Protocols included a combination of medications, such that percentages sum to more than 100%.

Figure 2: Bowel Protocol Initiation Criteria



Legend for Figure 2: The criteria cited for initiating bowel protocols are presented here. Some bowel protocols had more than one criterion for initiation. The bowel protocols did not define what “at risk for constipation” meant.

Table 1: Medication Escalation and Bowel Protocol Discontinuation Criteria

Criteria for Medication Escalation	**N (%)**
Time from last bowel movement	22 (59.4)
Opioid use	7 (18.9)
No stool on digital rectal exam	6 (16.2)
No criteria described	6 (16.2)
Criteria for Protocol Discontinuation	**N (%)**
Diarrhea	15 (40.5)

Legend for Table 1: The criteria incorporated for escalation of medication are presented here. Some bowel protocols had more than one criterion for escalation of therapy, such that percentages add up to more than 100%. Less than half of the bowel protocols had an explicit discontinuation criterion.

Table 2: Contraindications to Bowel Protocols

Contraindications	**N (%)**
Renal disease	8 (21.6)
Major abdominal surgery/bowel obstruction	8 (21.6)
Neutropenia (or bone marrow transplant)	5 (13.5)
Nausea and vomiting, undiagnosed abdominal pain	4 (10.8)
Platelet count < 50,000 x 10^9/L	2 (5.2)
Fecal impaction	1 (2.7)

Legend for Table 2: Contraindications to bowel protocols are presented here. Some bowel protocols had more than one contraindication criterion.

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None of the authors disclose any competing interests.

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Supplement-Table 1: PROSPECT Centers With and Without Bowel Protocols

Hospital	Type of ICU	Community or Academic	Number of beds	Bowel Protocol
Canada				
St. Joseph's Healthcare Hamilton, Hamilton, ON	Medical, Surgical	Academic	21	Yes
Hamilton General Hospital, Hamilton, ON	Medical, Surgical, Trauma, Neurosurgery	Academic	31	Yes
Juravinski Hospital, Hamilton, ON	Medical, Surgical	Academic	23	Yes
St. Michael's Hospital, Toronto, ON	Medical, Surgical, Trauma, Neurosurgery	Academic	24	Yes
Mount Sinai Hospital, Toronto, ON	Medical, Surgical	Academic	16	No
The Ottawa Hospital, Civic Campus Ottawa, ON	Medical, Surgical, Trauma, Neurosurgery	Academic	26	Yes
The Ottawa Hospital, General Campus, Ottawa, ON	Medical, Surgical, Trauma	Academic	25	Yes
University Health Network, Toronto Western Hospital, Toronto, ON	Medical, Surgical, Trauma, Neurosurgery	Academic	24	No
University Health Network, Toronto General Hospital, Toronto, ON	Medical, Surgical	Academic	28	Yes
Kingston General Hospital, Kingston, ON	Medical, Surgical, Trauma, Neurosurgery	Academic	33	Yes
London Health Science Centre, Victoria Hospital, London, ON	Medical, Surgical, Trauma, Neurosurgery	Academic	29	Yes
London Health Science Centre, University Hospital, London, ON	Medical, Surgical	Academic	19	Yes
Brantford General Hospital, Brantford, ON	Medical, Surgical	Community	15	Yes

Hospital	Type of ICU	Community or Academic	Number of beds	Bowel Protocol
St. Joseph's Health Center, Toronto, ON	Medical, Surgical	Community	20	Yes
William Osler, Brampton Civic Hospital, Brampton, ON	Medical, Surgical	Community	44	Yes
Niagara Health, St Catharine's Hospital, St. Catharine's, ON	Medical, Surgical	Community	14	Yes
Grand River Hospital, Kitchener, ON	Medical, Surgical	Community	20	Yes
Sunnybrook Hospital, Toronto, ON	Medical, Surgical, Trauma, Neurosurgery	Academic	34	Yes
Joseph Brant Hospital, Burlington, ON	Medical, Surgical	Community	20	Yes
Hôpital de l'Enfant-Jésus, Québec City, QC	Medical, Surgical, Trauma, Neurosurgery	Academic	29	Yes
Hôpital du Sacré-Cœur de Montréal, QC	Medical, Surgical, Trauma, Neurosurgery	Academic	36	Yes
Centre Hospitalier Universitaire de Sherbrooke (CHUS), Sherbrooke, QC	Medical, Surgical, Trauma, Neurosurgery	Academic	44	No
Hôpital Royal Victoria, Montreal, QC	Medical, Surgical	Academic	30	No
Montreal General Hospital, Montreal, QC	Medical, Surgical, Trauma	Academic	22	No
Hôpital Notre Dame, Montréal, QC	Medical, Surgical, Neurosurgery	Academic	16	No
Hôpital Saint-Luc, Montreal, QC	Medical, Surgical	Academic	14	No
The Centre hospitalier de l'Université de Montréal (N-CHUM), Montreal, QC	Medical, Surgical, Neurosurgery	Academic	60	No
Hôpital Maisonneuve-Rosemont, Montréal, QC	Medical, Surgical	Academic	16	Yes

Hospital	Type of ICU	Community or Academic	Number of beds	Bowel Protocol
Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval, Québec City, QC	Medical, Surgical	Academic	35	Yes
Hôtel-Dieu de Lévis Hôpital, Québec City, QC	Medical, Surgical	Community	18	Yes
St Paul's Hospital, Vancouver, BC	Medical, Surgical	Academic	19	Yes
Vancouver General Hospital, Vancouver, BC	Medical, Surgical, Trauma, Neurosurgery	Academic	34	Yes
Vancouver Island Health Authority, Victoria, BC	Medical, Surgical, Trauma	Academic	20	Yes
Royal Columbia Hospital, New Westminster, BC	Medical, Surgical	Academic	16	Yes
University of Alberta Hospital, Edmonton, AB	Medical, Surgical, Trauma	Academic	32	No
Foothills Medical Center, Calgary, AB	Medical, Surgical, Trauma	Academic	28	Yes
Peter Lougheed Hospital, Calgary, AB	Medical, Surgical	Academic	22	Yes
Royal Alexandra Hospital, Edmonton, AB	Medical, Surgical, Trauma	Academic	27	No
St. Boniface Hospital, Winnipeg, MB	Medical, Surgical	Academic	13	Yes
Health Science Centre Winnipeg, Winnipeg, MB	Medical, Surgical, Trauma, Neurosurgery	Academic	27	Yes
QEII Health Science Center, Halifax, NS	Medical, Surgical, Trauma, Neurosurgery	Academic	21	Yes
United States of America				
Mayo Clinic, Rochester, MN	Medical, Surgical	Academic	24	No
Mercy Medical Center, St. Louis, MO	Medical, Surgical, Trauma	Academic	54	Yes
Saudi Arabia				

Hospital	Type of ICU	Community or Academic	Number of beds	Bowel Protocol
King Abdulaziz Medical City, Riyadh, SA	Medical, Surgical, Trauma	Academic	60	Yes

Legend for Table 1 (supplement): Listed here are the characteristics of participating centers, including type of ICU, number of ICU beds, type of ICU, setting and presence or absence of bowel protocols.

Chapter 5

Clostridioides Difficile Infection in Mechanically Ventilated Critically Ill Patients: A Nested Cohort Study

Clostridioides difficile infection in Mechanically Ventilated Critically Ill Patients: A Nested Cohort Study

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Abstract

Introduction: *Clostridioides difficile* infection (CDI) is associated with significant morbidity and mortality in the intensive care unit (ICU). Our objective was to determine the frequency, timing, severity, predictors, impact and treatment of CDI among critically ill patients enrolled in a randomized trial.

Methods: We performed a nested cohort study of CDI within an international randomized trial comparing the probiotic *Lactobacillus rhamnosus GG* to placebo in mechanically ventilated patients to evaluate pneumonia and other ICU-acquired infections including CDI (PROSPECT, NCT02462590). To identify patients with possible CDI, we collected daily data regarding diarrhea during the ICU admission and all *C. difficile* testing during hospital admission. We conducted blinded duplicate adjudication of all patients with possible CDI, using standardized definitions to diagnose CDI, determine timing (pre-ICU, in ICU, post-ICU), rate severity (comparing the American College of Gastroenterology, Society for Healthcare Epidemiology of America (SHEA)-Infectious Diseases Society of America (IDSA), and the European Society of Clinical Microbiology and Infections Disease criteria), analyze risk factors, describe treatments, and assess hospital mortality and length of stay.

Results: Of 2650 mechanically ventilated patients enrolled in PROSPECT, 86 were diagnosed with CDI over 90,833 hospital-days, generating a rate of 9.5 per 10,000 hospital-days and a CDI prevalence of 3.2% (95% confidence interval [CI] 2.6% to 4.0%). Nine (0.3%) patients were identified with CDI pre-ICU, and 57 (2.2%) developed CDI in the ICU, with a rate of 1.3 per 1000 ICU-days. An additional 20 (0.8%) patients developed CDI post-ICU. Hospital-based CDI relapse or reoccurrence occurred in 8 of 86 (9.3%) patients. The majority of infections were mild to moderate in severity consistently scored across all three severity systems; 58 (68.2%) having mild to moderate disease based on SHEA, 65 (76.5%) based on ACG and 71 (83.5%) based on the ESCMID. A minority of patients had severe CDI: 18 (21.2%, SHEA), 8 (9.4%, ACG), and 14 (16.5%, ESCMID). There were only 9 (10.6%) and 12 (14.1%) patients with severe, complicated CDI based on SHEA and ACG scores, respectively agreement among severity scores was fair to moderate (range of 2-way kappas 0.47 to 0.64). Complications of CDI included septic shock (23, 26.7%), end-organ failure (14, 16.3%), toxic megacolon (1, 1.2%) requiring a colectomy. Among patients with and without CDI, crude hospital mortality was 27.3% versus 28.0%, respectively; however, CDI was not independently associated with hospital mortality (HR 0.97; 95% CI 0.58-1.63, p=0.916) after adjusting for the APACHE II score. Patients with CDI stayed in hospital a mean of 42 days (IQR 22,77) compared to those without who stayed 22 days (IQR 12,40), p<0.001). Adjusting for APACHE II score, randomized group, medical/surgical/trauma admitting diagnosis, and center in linear regression, this difference remained significant (p<0.001). Most patients received one or more of metronidazole (66, 76.7%), primarily

administered orally (48, 55.8%), and oral vancomycin (56, 65.1%). No patients received fidaxomicin. Fecal transplant was performed in 3 (3.5%) patients. No independent risk factor for CDI was identified.

Conclusion: Among mechanically ventilated patients enrolled in a probiotics trial, CDI was relatively uncommon and the severity was mild to moderate. We found no independent risk factors for CDI. CDI was not associated with an increased risk of hospital mortality but was associated with a significantly longer length of stay in hospital.

Introduction

Clostridioides difficile infection (CDI) is associated with significant morbidity and mortality [1] in hospitalized patients, with 462,100 cases annually in the United States. [2]. Community-acquired recurrence rates may be as high as 31,300 cases annually, and healthcare-associated rates are estimated at 38,500 cases annually[2]. The burden of CDI on the healthcare system is significant, costing approximately $8,911 USD to $30,049 USD per hospitalized patient [3] with an estimated annual cost of 1.1 to 3.2 billion USD per year [4]. A Canadian provincial study in Alberta found that the mean attributable cost per case was $18,386 (CAD 2018; USD $14,190; 95% CI, $14,312-$22,460; USD $11,046-$17,334) [5].

With its impact on patients and the healthcare system, CDI has been a focus of health research in areas such as epidemiology, therapeutics, and infection control. However, most CDI research consists of retrospective cohort, cross-sectional studies, and few studies have specifically examined the impact of CDI in the Intensive Care Unit (ICU). One retrospective matched cohort demonstrated that ICU-acquired CDI was

associated with increased length of ICU and hospital stay but not increased mortality [1]. Conflicting results have been generated in prior studies about CDI-associated mortality rates of 5.5% to 6.9% in hospitalized patients[4, 6-11] .

The objectives of this study were to 1) analyze the incidence and prevalence of CDI in the ICU, 2) describe the timing of CDI (pre-ICU, in ICU, and post-ICU), 3) assess the severity of CDI using 3 scoring systems and understand the agreement among scores, 4) analyze CDI risk factors, 5) examine the hospital mortality and length of stay of patients with CDI compared to without CDI and 6) document CDI treatments used.

Methods

We performed a nested cohort study within a randomized controlled trial in 2,650 mechanically ventilated patients compared the probiotic *Lactobacillus rhamnosus* GG to placebo on the primary outcome of ventilator-associated pneumonia (PROSPECT, Probiotics to prevent Severe Pneumonia and Endotracheal Colonization Trial, NCT02462590)[12]. Other outcomes were other ICU-acquired infections including CDI, antimicrobial use, and diarrhea. Enrolled patients were at least 18 years old and expected to be mechanically ventilated for at least 72 hours. Patients were excluded if immunocompromized (HIV with a CD4 count less than 200 cells/μL, chronic immunosuppressive medications, chemotherapy in the last 3 months, prior organ or hematological transplant, or absolute neutrophil count less than 500 cells/μL); if they carried increased risk of endovascular infection; had severe acute pancreatitis; a percutaneous enteral feeding tube, were unable to receive enteral medication; had plans for palliation; and those previously enrolled in this trial or a related trial.

Daily all bowel movements were counted and characterized using the Bristol Stool Chart[13, 14]. For each enrolled patient, research coordinators recorded baseline data and daily clinical data (e.g., *Clostridioides difficile* testing, culture results, infections, treatments, diarrhea defined as Bristol Type 6 or 7), length of stay and mortality. For all patients who had a suspected or confirmed CDI, we collected additional information from the medical chart, and a CDI case report form (Appendix) was sent to the PROSPECT Methods Center. In this study, we used standardized definitions to define CDI as follows: laboratory confirmation of *C. difficile* together with three or more episodes of diarrhea within a 24-hour period[15].

Two independent adjudicators conducted blinded adjudication of patients with suspected CDI to categorize the timing of infection (pre-ICU, in ICU, post-ICU). We defined pre-ICU CDI if the diagnosis was made <72 hours of ICU admission or earlier. CDI was defined as being acquired in ICU if it was diagnosed 72 hours after ICU admission, and up to 72 hours after ICU discharge. We defined post ICU CDI if the diagnosis was made 72 hours after ICU discharge[15].

Adjudication was also used to assess whether it was a new infection, relapse, or recurrence, and rate the severity of infection using three severity scales (American College of Gastroenterology[16] , Society for Healthcare Epidemiology of America (SHEA)-Infectious Diseases Society of America (IDSA) [17], and the European Society of Clinical Microbiology and Infections Disease criteria[18]) (Box 1). We resolved any disagreement using a third adjudicator.

Analysis

We calculated measures of central tendency and dispersion. To identify new cases of CDI acquired only in ICU, we calculated incidence as the total number of expressed as both a percentage of the entire cohort and as a rate per 1000 ICU days. We defined period prevalence during the entire study by the number of patients with CDI (pre-ICU, ICU, post-ICU) expressed as a percentage and as a rate per 10,000 hospital-days.

We assessed the agreement between the three scoring systems using kappa statistics in pairwise comparison.

We examined risk factors for CDI identified in the ICU (excluding patients who had a) CDI diagnosed pre-ICU, b) CDI diagnosed in ICU prior to their third day in the PROSPECT study, or c) CDI diagnosed after discharge from ICU) using Cox regression, considering baseline illness severity as measured by APACHE II score as well as 3 time dependent exposures within the previous 3 days (vasopressors, antibiotics and stress ulcer prophylaxis with either histamine-2-receptor antagonists (H2RA) or proton pump inhibitors (PPI)), reporting adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CI) and p-values.

We examined the association between CDI identified after ICU admission (excluding patients who had CDI diagnosed pre-ICU) and hospital mortality by crude comparison, and using Cox regression, unadjusted and adjusted for the APACHE II score, reporting hazard ratios (HR) with corresponding 95% confidence intervals (CI) and p-values. We conducted a sensitivity analysis excluding prevalent CDI in the first 2 days.

We examined the association between CDI identified in the ICU (excluding patients who had CDI diagnosed pre-ICU) and the logarithm of hospital length of stay by crude comparison, reported using a t-test on the log-transformed variable. We also used linear regression, reporting results unadjusted and adjusted for APACHE II score, randomized group, medical/surgical trauma admitting diagnosis and center, showing median differences with corresponding interquartile ranges and p-values. We conducted a sensitivity analysis on survivors only.

We report treatment received as number and percentages. We conducted a secondary analyses of risk factors for CDI including APACHE II Score, histamine-2 receptor agonists (H2RA or proton pump inhibitors, antibiotic exposure, or vasopressor use, by using a Cox proportional hazards regression. All analyses were performed using SAS (version 9.4, 2013)[19].

Results

Among 2650 patients enrolled in this study, characteristics are shown in Table 1, including number of BMs and diarrhea, and the timing of CDI diagnosis. Overall, 86 patients were diagnosed with CDI at any point during the study, which comprised 90,883 hospital-days. This corresponds to a rate of 9.5 per 10,000 hospital-days and a study prevalence of 3.2% (95% CI 2.6% to 4.0%). A total of 9 (0.3%) patients developed CDI prior to ICU admission and 57 (2.2%) developed CDI during 43,927 ICU-days, corresponding to a rate of 1.3 per 1000 ICU-days. In contrast, 20 (0.8%), patients were found to have CDI following ICU discharge. A relapse or recurrence of CDI was found in 8 of 86 patients (9.3%) patients. Complications of CDI included septic shock (23,

26.7%), end organ failure (14, 16.3%), and toxic megacolon that required colectomy (1, 1.2%).

The most common diagnostic test used to help identify CDI was nucleic acid amplification test (NAAT)-based assays; polymerase chain reaction (PCR) (50, 58.1%) or loop mediated isothermal amplifications (LAMP) (23, 26.7%), with one patient having 2 diagnostic tests. Only a minority used exclusively enzyme linked immunosorbent assay (ELISA) testing (12, 14.0%) or other tests (2, 2.3%).

The majority of infections were mild to moderate in severity consistently scored across all three severity systems (Table 2), with 58 (68.2%) having mild to moderate disease based on SHEA, 65 (76.5%) based on ACG and 71 (83.5%) based on the ESCMID. A minority of patients had severe CDI: 18 (21.2%, SHEA), 8 (9.4%, ACG), and 14 (16.5%, ESCMID). There were only 9 (10.6%) and 12 (14.1%) patients with severe, complicated CDI based on SHEA and ACG scores, respectively.

Agreement between the ACG and SHEA scores (Table 3) (Kappa 0.63, 95% CI 0.46 to 0.80) and the ESCMID compared to ACG (Kappa 0.64, 95% CI 0.43 to 0.84) was moderate. The agreement between the ESCMID and the SHEA score was fair (Kappa 0.47, 95% CI 0.27 to 0.67). The hospital length of stay and hospital mortality of patients with CDI across all severity scores is displayed in Table 4.

Associations with CDI documented in the Cox regression included APACHE II score (HR 0.83, 95% CI 0.55-1.25), p=0.372), receipt of stress ulcer prophylaxis (HR 1.28 (0.39, 4.21) p=0.686), antibiotics (1.24 (0.50, 3.06), p=0.647) and vasopressors or inotropes (HR 1.09 (0.57, 2.11), p=0.790) (Table 5). None of these were statistically significant[11].

Among patients with and without CDI, crude hospital mortality was 27.3% versus 28.0%, respectively; however, CDI was not independently associated with hospital mortality (HR 0.97; 95% CI 0.58, 1.63, p=0.916) after adjusting for the APACHE II score (Table 6). The sensitivity analysis excluding prevalent CDI in the first 2 days yielded a HR of 1.15 (95% CI 0.63, 2.11).

Patients with CDI stayed in hospital a mean of 42 days (IQR 22,77) compared to those without who stayed 22 days (IQR 12,40), p<0.001). Adjusting for APACHE II score, randomized group, medical/surgical/trauma admitting diagnosis, and center in linear regression, this difference remained significant (p<0.001). Results were similar in a sensitivity analysis including only survivors (p<0.001). (Table 7).

Treatments received included metronidazole (66, 76.7%), most often orally (48, 55.8%), oral vancomycin (56, 65.1%). No patients received fidaxomicin. Fecal transplant was performed in 3 (3.5%) patients.

Discussion

This secondary analysis of critically ill patients enrolled in the PROSPECT randomized trial demonstrated that most critically ill patients develop this infection while they are in the ICU, but some infections are comorbidities before critical illness, and some infections are only evident as in the recovery phase after ICU discharge. CDI acquired in ICU was mild to moderate in severity according to 3 pre-existing criteria, with the most common complication being septic shock. The most common treatment was metronidazole, reflective of guideline recommendations at the time of trial conduct [17]. The agreement between the severity ratings was fair to moderate.

The incidence of CDI we documented of 2.2% is in keeping with other studies reporting CDI incidence in critically ill patients [20]. Our study showed a 3.2% prevalence of CDI in this cohort that was higher than some other studies[20] however in one retrospective cohort study, an incidence of ICU-acquired CDI has been reported as high as 3.2 cases per 1,000 patient days[21]. Karanika and colleagues [20] conducted a systematic review of 80,835 ICU patients and found a CDI prevalence of 2%; [20]. In comparison, another systematic review of CDI in hospitalized patients showed that the incidence across 13 studies ranged from 2.8 to 15.8 cases per 10,000 patient days [22]. Capturing the true incidence of CDI is challenging in clinical studies due to variability in definitions and testing strategies.

Other studies have sought to determine the incidence, prevalence, risk factors and outcomes for CDI in the hospital [8, 9, 11] and in the ICU [1, 21] prolonged hospitalization[17], chemotherapy, enteral nutrition[17, 23] and proton pump inhibitors (PPI). However, data are conflicting as recent data do not show that exposure to PPIs increases the risk of CDI, and the prior signal may be as a result of confounding[17, 24, 25]. These CDI risk factors are particularly relevant to critically ill patients, who are at increased risk of many ICU-acquired infections, including CDI.

We documented fair agreement across all CDI severity scoring systems. Few studies have compared the severity of CDI across scoring systems. One study examined the differences in severity scores in classifying disease severity in patients with CDI using the IDSA and ACG scoring systems in their ability to predict colectomy and mortality[26]. A retrospective cohort study of 894 patients with CDI found that the ACG score labelled more patients as severe and complicated compared to the IDSA

definition [26], possibly because the former includes many non-specific illness severity parameters[16] Although the IDSA [17] severity metric includes a WBC count, ileus or megacolon criterion, it also includes acute kidney injury which is non-specific and common during critical illness. Ensuring consistent nomenclature in practice will improve interprofessional recognition of CDI severity. Given the complexities of critical illness, an ICU-specific metric for CDI severity in this population may be warranted to better risk stratify these patients.

We found that patients with CDI had a similar hospital mortality compared to other patients. Prior research yielded conflicting results regarding the association of CDI with mortality. The hospital mortality observed in this critically ill population for those with CDI was 27.3%. One systematic review [20] of CDI in ICU patients showed a hospital mortality of 32%, compared to 24% in patients without CDI [20]. Manthey and colleagues conducted a retrospective cohort study of 144 patients with CDI found that 28 day mortality in critically ill patients with CDI to be 27.3% compared to 9.0% in non-CDI patients[[27]. The difference seen in our study may be attributed to the larger sample size of our study, prospective design, and potentially sicker patients at baseline given trial enrollment criteria including dependence on mechanical ventilation[12, 28] .

Other studies have examined the impact of CDI on length of stay compared to patients without CDI in critically ill patients. In one review [20], critically ill patients with CDI had longer length of stay in ICU and hospital compared to those whose without CDI [20], underscoring the economic impact for the health care system. We also found a significant association between CDI and hospital length of stay which cannot be interpreted as causation in this observational study. This could mean that CDI

increases the hospital length of stay, but could also reflect how being in hospital increases the risk of CDI. Another explanation is that the risk factors for a longer hospital length of stay also increase the risk of developing CDI. From an economic perspective, patients with CDI require isolation in single rooms and consumables for infection control purposes; the increased length of stay for patients with CDI is a further indication of associated healthcare costs.

The treatment for CDI reflects guideline recommendations for the treatment of CDI from 2013 to 2019 during the years of patient enrolment. Antimicrobial guidelines for first CDI occurrence in 2010 recommended metronidazole as first line for mild to moderate CDI [17], then oral vancomycin in 2017 [29], and in 2021, fidaxomicin [2].

The strengths of our study include the large sample size, prospective enrolment of critically ill patients, documentation of the number and characteristics of all bowel movements, rigorous methodology with blinded adjudication of the CDI microbiologic data and outcomes, and application of three validated scores to assess CDI severity. Patients had heterogeneous diagnoses and were enrolled in 3 countries, thereby enhancing the generalizability of our findings. However, this study has limitations. We do not have data on the prevalence of NAP1/B1/027 hypervirulent strains. Findings in this study for CDI antimicrobial treatment reflect these changes in practice over time. Although characteristics of patients with and without CDI are demonstrated, the relatively low CDI event rate means that other unmeasured confounders could have affected the multivariate analyses of CDI risk factors and analysis of attributable mortality and length of stay. This cohort was determined by participants in a randomized trial of probiotics, focused on patients expected to be mechanically

ventilated for at least 72 hours; therefore, our results do not represent critically ill patients with a short stay in the ICU.

Conclusion

We found that CDI was relatively uncommon in this population of mechanically ventilated critically ill patients. When acquired in the ICU, CDI severity was mild to moderate and most patients received metronidazole, reflecting guideline recommendations at the time. No independent risk factors were identified. Future research of CDI in the critically ill should focus on developing an ICU-specific metric to characterize CDI severity.

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Box 1: Definitions of CDI Severity

	SHEA[17]	ACG[16]	ESCMID[18]
Mild to Moderate CDI	WBC < 15x109/L AND Creatinine <1.5 x premorbid level	Diarrhea PLUS signs and symptoms not meeting the criteria for sever or complicated	A clinical picture compatible with CDI and microbiological evidence of free toxins and the presence of CDI in stool without reasonable evidence of another cause of diarrhea OR Pseudomembranous colitis as diagnosed during endoscopy, after colectomy or autopsy
Severe	WBC > $15x10^9$/L Creatinine > 1.5 X Premorbid level	Serum Albumin <30g/L PLUS one of the following: WBC > $15x10^9$/L Abdominal tenderness	An episode of CDI with one or more specific signs and symptoms of severe colitis or complicated course of disease with significant systemic toxin effects and shock, resulting in the need for ICU admission, colectomy or death
Severe with complications	Hypotension Shock Ileus Megacolon	Any of the following attributable to CDI: Hypotension with vasopressors Fever > 38.5°C Ileus or significant abdominal distention Mental status changes WBC > $35x10^9$/L or <$2x10^9$/L	

		Lactate> 2.2 mmol/L End-organ failure (ex. New mechanical ventilation or dialysis	

Legend for Box: These are the definitions from the clinical practice guidelines cited above.

Table 1: Patient Characteristics

Characteristics	**Patients without CDI n=2564**	**Patients with CDI n=86**	**Total n=2650**
Age in years, mean (SD)	59.8 (16.5)	60.7 (15.4)	59.8 (16.5)
APACHE II, mean (SD)	22.0 (7.8)	23.0 (7.1)	22.0 (7.8)
Clinical Frailty Score† mean (SD) ≥5, number (%)	 3.4 (1.6) 450/2116 (21.3)	 3.9 (1.5) 22/66 (33.3)	 3.4 (1.6) 472/2182 (21.6)
Females, n (%)	1018 (39.7)	45 (52.3)	1063 (40.1)
Type of Patient, number (%) Medical Surgical Trauma	 1954 (76.2) 265 (10.3) 345 (13.5)	 73 (84.9) 5 (5.8) 8 (9.3)	 2027 (76.5) 270 (10.2) 353 (13.3)
Admitting Diagnosis, number (%) Respiratory Neurologic Trauma Sepsis Cardiovascular Gastrointestinal Metabolic Renal Cardiovascular surgery Hematologic Orthopedic Gynecologic Other Medical Other Surgical	 888 (34.6) 456 (17.8) 355 (13.8) 307 (12.0) 243 (9.5) 103 (4.0) 88 (3.4) 28 (1.1) 11 (0.4) 5 (0.2) 3 (0.1) 2 (0.1) 39 (1.5) 36 (1.4)	 29 (33.7) 13 (15.1) 9 (10.5) 19 (22.1) 5 (5.8) 1 (1.2) 6 (7.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 4 (4.7) 0 (0.0)	 917 (34.6) 469 (17.7) 364 (13.7) 326 (12.3) 248 (9.4) 104 (3.9) 94 (3.5) 28 (1.1) 11 (0.4) 5 (0.2) 3 (0.1) 2 (0.1) 43 (1.6) 36 (1.4)
Study Day 1			
Inotropes or vasopressors	1567 (61.1)	54 (62.8)	1621 (61.2)
Renal replacement therapy	202 (7.9)	13 (15.1)	215 (8.1)
H2RA or PPI	2320 (90.5)	83 (96.5)	2403 (90.7)
Antibiotics	2113 (82.4)	73 (84.9)	2186 (82.5)
Baseline Antibiotics			
On day of randomization or within 2 days prior	2218 (86.5)	75 (87.2)	2293 (86.5)
On day of randomization AND day prior AND day prior to that (used in our subgroup analysis)	1106 (43.1)	39 (45.3)	1145 (43.2)

Legend for Table 1: In this table we present baseline characteristics of 2,650 critically ill patients. SD=standard deviation. APACHE=Acute Physiology and Chronic Health Evaluation II Score. † n=2182. Pre-Hospital Admission Clinical Frailty Scale Form 3B became mandatory for patients randomized on or after May 2016.

Table 2: Severity of CDI infection

	SHEA/IDSA	ACG	ESCMID
Mild/moderate	58 (68.2)	65 (76.5)	71 (83.5)
Severe	18 (21.2)	8 (9.4)	14 (16.5)
Severe with complications	9 (10.6)	12 (14.1)	N/A

Legend for Table 2: Number (%) of the 85 patients with CDI infection. Above reflects the highest severity per patient.

Table 3: Agreement between CDI Severity Scores

		SHEA/IDSA		
		Mild/moderate	Severe	Severe with Complications
ACG	Mild/moderate	55	10	0
	Severe	1	7	0
	Severe with complications	2	1	9

Kappa = 0.63 (0.46, 0.80)
Weighted kappa = 0.76 (0.60, 0.92)

		SHEA/IDSA	
		Mild/moderate	Severe with or without Complications
ESCMID	Mild/moderate	56	15
	Severe	2	12

Kappa = 0.47 (0.27, 0.67)

		ACG	
		Mild/moderate	Severe with or without Complications
ESCMID	Mild/moderate	63	8
	Severe	2	12

Kappa = 0.64 (0.43, 0.84)

Legend for Table 3: In this series of tables, we present the CDI severity classification according to different severity metrics, and agreement statistics between severity scores.

Table 4: Relationship Between CDI Severity Scores and Hospital Length of Stay and Mortality

CDI Severity Score	Number of Patients	Hospital LOS (%)	Hospital Mortality (%)
SHEA			
Mild/moderate	58	8 (13.8)	17 (29.3)
Severe	18	4 (22.2)	4 (22.2)
Severe with complications	9	4 (44.4)	5 (55.6)
ACG			
Mild/moderate	65	9 (13.8)	17 (26.2)
Severe	8	3 (37.5)	3 (37.5)
Severe with complications	12	4 (33.3)	6 (50.0)
ESCMID			
Mild/moderate	71	12 (16.9)	20 (28.2)
Severe	14	4 (28.6)	6 (42.9)

Legend for Table 4: In this table we present hospital length of stay and hospital mortality rates for patients with CDI across different severity ratings across three severity scores.

Table 5 Risk Factors for CDI

	Hazard Ratio (95% CI)	P-value
Baseline characteristics		
APACHE II (10-point increase)	0.83 (0.55, 1.25)	0.372
Time-dependent factors (in the preceding 3 days)		
H_2RA and/or PPI	1.28 (0.39, 4.21)	0.686
Antibiotics	1.24 (0.50, 3.06)	0.647
Vasopressors or inotropes	1.09 (0.57, 2.11)	0.790

Legend for Table 5: In this table we present the Cox proportional hazards regression analysis results with incident *CDI* diagnosed in ICU as the outcome (study day 3 or later per main trial definition). This model includes n=2624 patients with 40 events. Patients with prevalent *C diff* infection (n=26) are excluded from this analysis. Because there are so few events, neither randomized group nor stratification by medical/surgical/trauma admitting diagnosis or center.

Table 6: Association of CDI and Mortality

	Patients without CDI n=2564	Patients With CDI n=77	Total n=2641	Adjusted Hazard Ratio (95% CI)	P-value
Death in hospital, N patients (%)	718 (28.0)	21 (27.3)	739 (28.0)	0.97 (0.58, 1.63)	0.916
Sensitivity Analysis: Excluding patients with prevalent *CDI*	Patients without CDI n=2564	Patients with CDI n=60	Total n=2624	Adjusted Hazard Ratio (95% CI)	P-value
Death in hospital, N patients (%)	718 (28.0)	16 (26.7)	734 (28.0)	1.15 (0.63, 2.11)	0.645

Legend for Table 6: In this table, we present the Cox regression analysis results with hospital mortality as the outcome. Patients with *C diff* infection diagnosed prior to ICU admission (n=9) are excluded from this analysis. This model includes n=2641 patients with 739 events. In this time-to-event analysis, the time starts on day of ICU admission. This analysis is adjusted for APACHE II score and randomized group, stratified by medical/surgical/trauma and center. C diff infection is entered as a time-dependent variable.

Table 7: Association of CDI on Length of Stay

	Patients without CDI n=2564	Patients With CDI n=77	Total n=2641	P-value – unadjusted analysis*	P-value – from linear regression†
All Patients					
Duration of hospital stay in days median (Q1-Q3) total range	22 (12-40) 1-630	42 (22-77) 7-334	22 (13-41) 1-630	<0.001	<0.001
Sensitivity Analysis: Only patients discharged alive from hospital	Patients without CDI n=1846	Patients With CDI n=56	Total n=1902	P-value – unadjusted analysis	P-value – from linear regression
Duration of hospital stay in days median (Q1-Q3) total range	25 (14-44) 2-630	45 (29-84.5) 8-288	25 (15-46) 2-630	<0.001	<0.001

Legend for Table 7: In this table, we present the association between CDI identified in the ICU (excluding patients who had CDI diagnosed pre-ICU) and the logarithm of hospital length of stay by crude comparison (* t-test performed on the log-transformed variable). We also show this association analyzed by linear regression presenting results unadjusted and adjusted for APACHE II score, randomized group, medical/surgical trauma admitting diagnosis and center, reporting unadjusted and adjusted mean differences with corresponding 95% confidence intervals (CI) and p-values. We conducted a sensitivity analysis in ICU survivors.

Appendix – CDAD Consent Release Form

PROSPECT Main RCT 076 Plate #360 Study Day

Patient ID 1 Patient Initials Date of Study Day (dd/mm/yyyy) 201

CLOSTRIDIUM DIFFICILE - ADJUDICATION FORM

Committee Member: ☐ DJC ☐ ED ☐ JD ☐ JJ

Timing of outcome: (Check all that apply)
☐ Pre-PROSPECT randomization
☐ Post-PROSPECT randomization, in ICU
☐ Post-PROSPECT randomization, post ICU

1. Please provide date of corresponding POSITIVE *Clostridium difficile* microbiological testing: Date (dd/mm/yyyy) 201

2. Which test was the *Clostridium difficile* based upon (Please check ALL that apply)?
☐ ELISA (enzyme-linked immunosorbent assay)
☐ PCR (polymerase chain reaction)
☐ Cell Culture Cytotoxicity Assay
☐ LAMP (loop-mediated isothermal amplification)
☐ Other, specify: _____

3. *Clostridium difficile* infection? ☐ No ☐ Yes, specify:
☐ ≥ 3 episodes of unformed stools in ≤24 hours
AND ☐ rectal tube in place (hard to quantify)
☐ *Clostridium difficile* toxin positive stool
OR ☐ Colonscopic findings demonstrating pseudomembranous colitis
OR ☐ Histopathological findings of pseudomembranous colitis
OR ☐ Diagnosis of toxic megacolon

4. Were any of the following present?	**No**	**Yes**	**If present, in the Adjudicators Opinion is this likely attributable *C. Diff* Infection? No**	**Yes**
ICU admission for this reason	☐	☐ →	☐	☐
Mental status changes	☐	☐ →	☐	☐
Fever >38.5°C	☐	☐ →	☐	☐
WBC ≥35.0 or <2.0 x 10^9/L	☐	☐ →	☐	☐
Lactate > 2.2 mmol/L	☐	☐ →	☐	☐
Septic shock (hypotension with vasopressors)	☐	☐ →	☐	☐
Ileus or significant abdominal distention	☐	☐ →	☐	☐
Toxic megacolon	☐	☐ →	☐	☐
Bowel perforation	☐	☐ →	☐	☐
End organ failure (i.e., new mechanical ventilation, dialysis)	☐	☐ →	☐	☐

5. Laboratory (If not available on day of event, record worst value 48 hours pre to 48 hours post event):
Results required only if positive for *C. difficile*

Highest WBC count 10^9/L on day of event ____.__
Highest lactate (mmol/L) on day of event ____.__
Lowest serum albumin (g/L) on day of event ____
Baseline creatinine (umol/L) ____
Highest creatinine (umol/L) on day of event ____

6. *Clostridium difficile* Infection Severity Classification, in the Adjudicators Opinion (Check one ONLY)
☐ Not *C diff* infection ☐ Mild to Moderate ☐ Severe ☐ Severe with complication (see list, questions 4 and 5)

And, if applicable indicate: (Check one ONLY)
☐ Recurrence (within 8 weeks of last *C diff episode* providing symptoms resolved after treatment)
☐ Relapse (same proven strain)

PROSPECT Main RCT 076 Plate #361

Study Day

Patient ID 1

Patient Initials

Date of Study Day (dd/mm/yyyy) 201

CLOSTRIDIUM DIFFICILE - ADJUDICATION FORM

Committee Member: [X] DJC [ ] ED [ ] JD [ ] JJ

7. Treatment (ever for this event)

- [ ] Antibiotic therapy started, specify ▸
  - [ ] metronidazole — PO [ ] IV [ ] enema [ ]
  - [ ] vancomycin — PO [ ] IV [ ]
  - [ ] fidaxomicin — PO [ ] IV [ ]
- [ ] Fecal transplant
- [ ] Colectomy
- [ ] Randomized CDI treatment trial, specify: _____
- [ ] NONE [ ] N/A
- [ ] Other, specify: _____

8. Clostridium difficile Infection Severity (Check ALL that apply): [ ] N/A NOT a *C. Difficile* Infection

	SHEA	ACG	ESCMID
Mild - Moderate	[ ] **SHEA - Mild to Moderate** (check all that apply): [ ] WBC ≤ $15x10^9$/L **AND** [ ] Creatinine < 1.5 X premorbid level	[ ] **ACG - Mild to Moderate** (check all that apply): [ ] Diarrhea **PLUS** signs and symptoms **NOT** meeting the criteria for severe or complicated	[ ] **ESCMID - Mild to Moderate** (check all that apply): [ ] A clinical picture compatible with CDI and microbological evidence of free toxins and the presence of *C. Diff* in stool without reasonable evidence of another cause of diarrhea **OR** [ ] Pseudommembraneous colitis as diagnosed during endo-scopy, after collectomy or on autopsy
Severe	[ ] **SHEA - Severe** (check all that apply): [ ] WBC ≥ $15x10^9$/L **OR** [ ] Creatinine ≥ 1.5 X premorbid level	[ ] **ACG- Severe** (check all that apply): [ ] Serum albumin <30g/L **PLUS one of the following:** [ ] WBC ≥ $15x10^9$/L [ ] Abdominal tenderness	[ ] **ESCMID - Severe** (check all that apply): [ ] An episode of CDI with **(one or more specific signs and symptoms of)** severe colitis [see table] or a complicated course of disease with significant systemic toxin effects and shock, resulting in the need for ICU admission, colectomy or death
Severe with Complication	[ ] **SHEA - Severe with complication** (check all that apply): [ ] Hypotension [ ] Shock [ ] Ileus [ ] Megacolon	[ ] **ACG - Severe with complication** (check all that apply): **Any of the following attributable to CDI:** [ ] Hypotension with vasopressors [ ] Fever ≥ 38.5°C [ ] Ileus or significant abdominal distention [ ] Mental status changes [ ] WBC ≥ $35x10^9$/L or <$2x10^9$/L [ ] Lactate > 2.2 mmol/L [ ] End-organ failure (i.e., new mechanical ventilation, dialysis)	

9. Comments:

CHARACTERISTICS OF SEVERE COLITIS

Patient Characteristics that could reasonably be assumed to correlate positively with severity of colitis in the absense of another explantion for these findings:

Category	Signs/symptoms
Physical examination	Fever (core body temperature >38.5°C). Rigors (uncontrollable shaking and a feeling of cold followed by a rise in body temperature). Haemodynamic instability including signs of distributive shock. Respiratory failure requiring mechanical ventilation. Signs and symptoms of peritonitis. Signs and symptoms of colonic ileus. Admixture of blood with stools is rare in *Clostridium difficile* infection (CDI) and the correlation with severity of disease is uncertain.
Laboratory investigations	Marked leucocytosis (leucocyte count >15 × 10^9/L). Marked left shift (band neutrophils >20% of leucocytes). Rise in serum creatinine (>50% above the baseline). Elevated serum lactate (≥5 mM). Markedly reduced serum albumin (<30 g/L).
Colonoscopy or sigmoidoscopy	Pseudomembranous colitis. There is insufficient knowledge on the correlation of endoscopic findings compatible with CDI, such as oedema, erythema, friability and ulceration, and the severity of disease.
Imaging	Distension of large intestine (>6 cm in transverse width of colon). Colonic wall thickening including low-attenuation mural thickening. Pericolonic fat stranding. Ascites not explained by other causes. The correlation of haustral or mucosal thickening, including thumbprinting, pseudopolyps and plaques, with severity of disease is unclear.

PROSPECT Main RCT 076 Plate #362

Study Day

Patient ID 1

Patient Initials

Date of Study Day (dd/mm/yyyy) 2 0 1

CLOSTRIDIUM DIFFICILE - ADJUDICATION FORM

Committee Member: ☐ DJC ☒ ED ☐ JD ☐ JJ

Timing of outcome: (Check all that apply)
- ☐ Pre-PROSPECT randomization
- ☐ Post-PROSPECT randomization, in ICU
- ☐ Post-PROSPECT randomization, post ICU

1. Please provide date of corresponding POSITIVE *Clostridium difficile* microbiological testing: Date (dd/mm/yyyy) 2 0 1

2. Which test was the *Clostridium difficile* based upon (Please check ALL that apply)?
- ☐ ELISA (enzyme-linked immunosorbent assay)
- ☐ PCR (polymerase chain reaction)
- ☐ Cell Culture Cytotoxicity Assay
- ☐ LAMP (loop-mediated isothermal amplification)
- ☐ Other, specify: _____

3. *Clostridium difficile* infection? ☐ No ☐ Yes, specify:
- ☐ ≥ 3 episodes of unformed stools in ≤24 hours
- **AND** ☐ rectal tube in place (hard to quantify)
- ☐ *Clostridium difficile* toxin positive stool
- **OR** ☐ Colonscopic findings demonstrating pseudomembranous colitis
- **OR** ☐ Histopathological findings of pseudomembranous colitis
- **OR** ☐ Diagnosis of toxic megacolon

4. Were any of the following present?

	No	Yes		If present, in the Adjudicators Opinion is this likely attributable *C. Diff* Infection? No	Yes
ICU admission for this reason	☐	☐	→	☐	☐
Mental status changes	☐	☐	→	☐	☐
Fever >38.5°C	☐	☐	→	☐	☐
WBC ≥35.0 or <2.0 x 10^9/L	☐	☐	→	☐	☐
Lactate > 2.2 mmol/L	☐	☐	→	☐	☐
Septic shock (hypotension with vasopressors)	☐	☐	→	☐	☐
Ileus or significant abdominal distention	☐	☐	→	☐	☐
Toxic megacolon	☐	☐	→	☐	☐
Bowel perforation	☐	☐	→	☐	☐
End organ failure (i.e., new mechanical ventilation, dialysis)	☐	☐	→	☐	☐

5. Laboratory (If not available on day of event, record worst value 48 hours pre to 48 hours post event):

Results required only if positive for *C. difficile*

Highest WBC count 10^9/L on day of event ____.____

Highest lactate (mmol/L) on day of event ____.____

Lowest serum albumin (g/L) on day of event ____

Baseline creatinine (umol/L) ____

Highest creatinine (umol/L) on day of event ____

6. *Clostridium difficile* Infection Severity Classification, in the Adjudicators Opinion (Check one ONLY)

☐ Not *C diff* infection ☐ Mild to Moderate ☐ Severe ☐ Severe with complication (see list, questions 4 and 5)

And, if applicable indicate: (Check one ONLY)

☐ Recurrence (within 8 weeks of last *C diff episode* providing symptoms resolved after treatment)

☐ Relapse (same proven strain)

PROSPECT Main RCT 076 Plate #363

Study Day

Patient ID 1

Patient Initials

Date of Study Day (dd/mm/yyyy) 201

CLOSTRIDIUM DIFFICILE - ADJUDICATION FORM

Committee Member: ☐ DJC ☒ ED ☐ JD ☐ JJ

7. Treatment (ever for this event)

- ☐ Antibiotic therapy started, specify ▸
  - ☐ metronidazole — PO ☐ IV ☐ enema ☐
  - ☐ vancomycin — PO ☐ IV ☐
  - ☐ fidaxomicin — PO ☐
- ☐ NONE ☐ N/A
- ☐ Other, specify: _____
- ☐ Fecal transplant
- ☐ Colectomy
- ☐ Randomized CDI treatment trial, specify: _____

8. Clostridium difficile Infection Severity (Check ALL that apply): ☐ N/A NOT a *C. Difficile* Infection

	SHEA	ACG	ESCMID
Mild - Moderate	☐ **SHEA - Mild to Moderate** (check all that apply): ☐ WBC ≤ $15x10^9$/L **AND** ☐ Creatinine < 1.5 X premorbid level	☐ **ACG - Mild to Moderate** (check all that apply): ☐ Diarrhea **PLUS** signs and symptoms **NOT** meeting the criteria for severe or complicated	☐ **ESCMID - Mild to Moderate** (check all that apply): ☐ A clinical picture compatible with CDI and microbological evidence of free toxins and the presence of *C. Diff* in stool without reasonable evidence of another cause of diarrhea **OR** ☐ Pseudommembraneous colitis as diagnosed during endo-scopy, after collectomy or on autopsy
Severe	☐ **SHEA - Severe** (check all that apply): ☐ WBC ≥ $15x10^9$/L **OR** ☐ Creatinine ≥ 1.5 X premorbid level	☐ **ACG- Severe** (check all that apply): ☐ Serum albumin <30g/L **PLUS one of the following:** ☐ WBC ≥ $15x10^9$/L ☐ Abdominal tenderness	☐ **ESCMID - Severe** (check all that apply): ☐ An episode of CDI with **(one or more specific signs and symptoms of)** severe colitis [see table] or a complicated course of disease with significant systemic toxin effects and shock, resulting in the need for ICU admission, colectomy or death
Severe with Complication	☐ **SHEA - Severe with complication** (check all that apply): ☐ Hypotension ☐ Shock ☐ Ileus ☐ Megacolon	☐ **ACG - Severe with complication** (check all that apply): **Any of the following attributable to CDI:** ☐ Hypotension with vasopressors ☐ Fever ≥ 38.5°C ☐ Ileus or significant abdominal distention ☐ Mental status changes ☐ WBC ≥ $35x10^9$/L or <$2x10^9$/L ☐ Lactate > 2.2 mmol/L ☐ End-organ failure (i.e., new mechanical ventilation, dialysis)	

9. Comments:

CHARACTERISTICS OF SEVERE COLITIS

Patient Characteristics that could reasonably be assumed to correlate positively with severity of colitis in the absense of another explantion for these findings:

Category	Signs/symptoms
Physical examination	Fever (core body temperature >38.5°C). Rigors (uncontrollable shaking and a feeling of cold followed by a rise in body temperature). Haemodynamic instability including signs of distributive shock. Respiratory failure requiring mechanical ventilation. Signs and symptoms of peritonitis. Signs and symptoms of colonic ileus. Admixture of blood with stools is rare in *Clostridium difficile* infection (CDI) and the correlation with severity of disease is uncertain.
Laboratory investigations	Marked leucocytosis (leucocyte count >15 × 10^9/L). Marked left shift (band neutrophils >20% of leucocytes). Rise in serum creatinine (>50% above the baseline). Elevated serum lactate (≥5 mM). Markedly reduced serum albumin (<30 g/L).
Colonoscopy or sigmoidoscopy	Pseudomembranous colitis. There is insufficient knowledge on the correlation of endoscopic findings compatible with CDI, such as oedema, erythema, friability and ulceration, and the severity of disease.
Imaging	Distension of large intestine (>6 cm in transverse width of colon). Colonic wall thickening including low-attenuation mural thickening. Pericolonic fat stranding. Ascites not explained by other causes. The correlation of haustral or mucosal thickening, including thumbprinting, pseudopolyps and plaques, with severity of disease is unclear.

PROSPECT Main RCT 076 Plate #364

Study Day

Patient ID 1

Patient Initials

Date of Study Day (dd/mm/yyyy) 2 0 1

CLOSTRIDIUM DIFFICILE - ADJUDICATION FORM

Committee Member: ☐ DJC ☐ ED ☒ JD ☐ JJ

Timing of outcome: (Check all that apply)
- ☐ Pre-PROSPECT randomization
- ☐ Post-PROSPECT randomization, in ICU
- ☐ Post-PROSPECT randomization, post ICU

1. Please provide date of corresponding POSITIVE *Clostridium difficile* microbiological testing: Date (dd/mm/yyyy) 2 0 1

2. Which test was the *Clostridium difficile* based upon (Please check ALL that apply)?
- ☐ ELISA (enzyme-linked immunosorbent assay)
- ☐ PCR (polymerase chain reaction)
- ☐ Cell Culture Cytotoxicity Assay
- ☐ LAMP (loop-mediated isothermal amplification)
- ☐ Other, specify: _____

3. *Clostridium difficile* infection? ☐ No ☐ Yes, specify:
- ☐ ≥ 3 episodes of unformed stools in ≤24 hours
- **AND** ☐ rectal tube in place (hard to quantify)
- ☐ *Clostridium difficile* toxin positive stool
- **OR** ☐ Colonscopic findings demonstrating pseudomembranous colitis
- **OR** ☐ Histopathological findings of pseudomembranous colitis
- **OR** ☐ Diagnosis of toxic megacolon

4. Were any of the following present?

	No	Yes	If present, in the Adjudicators Opinion is this likely attributable *C. Diff* Infection? No	Yes
ICU admission for this reason	☐	☐ →	☐	☐
Mental status changes	☐	☐ →	☐	☐
Fever >38.5°C	☐	☐ →	☐	☐
WBC ≥35.0 or <2.0 x 10^9/L	☐	☐ →	☐	☐
Lactate > 2.2 mmol/L	☐	☐ →	☐	☐
Septic shock (hypotension with vasopressors)	☐	☐ →	☐	☐
Ileus or significant abdominal distention	☐	☐ →	☐	☐
Toxic megacolon	☐	☐ →	☐	☐
Bowel perforation	☐	☐ →	☐	☐
End organ failure (i.e., new mechanical ventilation, dialysis)	☐	☐ →	☐	☐

5. Laboratory (If not available on day of event, record worst value 48 hours pre to 48 hours post event):

Results required only if positive for *C. difficile*

Highest WBC count 10^9/L on day of event ____.____

Highest lactate (mmol/L) on day of event ____.____

Lowest serum albumin (g/L) on day of event ____

Baseline creatinine (umol/L) ____

Highest creatinine (umol/L) on day of event ____

6. *Clostridium difficile* Infection Severity Classification, in the Adjudicators Opinion (Check one ONLY)

☐ Not *C diff* infection ☐ Mild to Moderate ☐ Severe ☐ Severe with complication (see list, questions 4 and 5)

And, if applicable indicate: (Check one ONLY)

☐ Recurrence (within 8 weeks of last *C diff episode* providing symptoms resolved after treatment)

☐ Relapse (same proven strain)

PROSPECT Main RCT 076 Plate #365

Study Day

Patient ID 1

Patient Initials

Date of Study Day (dd/mm/yyyy) 2 0 1

CLOSTRIDIUM DIFFICILE - ADJUDICATION FORM

Committee Member: ☐ DJC ☐ ED ☒ JD ☐ JJ

7. Treatment (ever for this event)

- ☐ Antibiotic therapy started, specify ▸
  - ☐ metronidazole — PO ☐ IV ☐ enema ☐
  - ☐ vancomycin — PO ☐ IV ☐
  - ☐ fidaxomicin — PO ☐ IV ☐
- ☐ NONE ☐ N/A
- ☐ Other, specify: _____
- ☐ Fecal transplant
- ☐ Colectomy
- ☐ Randomized CDI treatment trial, specify: _____

8. Clostridium difficile Infection Severity (Check ALL that apply): ☐ N/A NOT a *C. Difficile* Infection

	SHEA	ACG	ESCMID
Mild - Moderate	☐ **SHEA - Mild to Moderate** (check all that apply): ☐ WBC ≤ $15x10^9$/L **AND** ☐ Creatinine < 1.5 X premorbid level	☐ **ACG - Mild to Moderate** (check all that apply): ☐ Diarrhea **PLUS** signs and symptoms **NOT** meeting the criteria for severe or complicated	☐ **ESCMID - Mild to Moderate** (check all that apply): ☐ A clinical picture compatible with CDI and microbological evidence of free toxins and the presence of *C. Diff* in stool without reasonable evidence of another cause of diarrhea **OR** ☐ Pseudommembraneous colitis as diagnosed during endoscopy, after collectomy or on autopsy
Severe	☐ **SHEA - Severe** (check all that apply): ☐ WBC ≥ $15x10^9$/L **OR** ☐ Creatinine ≥ 1.5 X premorbid level	☐ **ACG- Severe** (check all that apply): ☐ Serum albumin <30g/L **PLUS one of the following:** ☐ WBC ≥ $15x10^9$/L ☐ Abdominal tenderness	☐ **ESCMID - Severe** (check all that apply): ☐ An episode of CDI with **(one or more specific signs and symptoms of)** severe colitis [see table] or a complicated course of disease with significant systemic toxin effects and shock, resulting in the need for ICU admission, colectomy or death
Severe with Complication	☐ **SHEA - Severe with complication** (check all that apply): ☐ Hypotension ☐ Shock ☐ Ileus ☐ Megacolon	☐ **ACG - Severe with complication** (check all that apply): **Any of the following attributable to CDI:** ☐ Hypotension with vasopressors ☐ Fever ≥ 38.5°C ☐ Ileus or significant abdominal distention ☐ Mental status changes ☐ WBC ≥ $35x10^9$/L or <$2x10^9$/L ☐ Lactate > 2.2 mmol/L ☐ End-organ failure (i.e., new mechanical ventilation, dialysis)	

9. Comments:

CHARACTERISTICS OF SEVERE COLITIS

Patient Characteristics that could reasonably be assumed to correlate positively with severity of colitis in the absense of another explantion for these findings:

Category	Signs/symptoms
Physical examination	Fever (core body temperature >38.5°C). Rigors (uncontrollable shaking and a feeling of cold followed by a rise in body temperature). Haemodynamic instability including signs of distributive shock. Respiratory failure requiring mechanical ventilation. Signs and symptoms of peritonitis. Signs and symptoms of colonic ileus. Admixture of blood with stools is rare in *Clostridium difficile* infection (CDI) and the correlation with severity of disease is uncertain.
Laboratory investigations	Marked leucocytosis (leucocyte count >15 × 10^9/L). Marked left shift (band neutrophils >20% of leucocytes). Rise in serum creatinine (>50% above the baseline). Elevated serum lactate (≥5 mM). Markedly reduced serum albumin (<30 g/L).
Colonoscopy or sigmoidoscopy	Pseudomembranous colitis. There is insufficient knowledge on the correlation of endoscopic findings compatible with CDI, such as oedema, erythema, friability and ulceration, and the severity of disease.
Imaging	Distension of large intestine (>6 cm in transverse width of colon). Colonic wall thickening including low-attenuation mural thickening. Pericolonic fat stranding. Ascites not explained by other causes. The correlation of haustral or mucosal thickening, including thumbprinting, pseudopolyps and plaques, with severity of disease is unclear.

PROSPECT Main RCT 076 Plate #366

Study Day

Patient ID 1

Patient Initials

Date of Study Day (dd/mm/yyyy) 2 0 1

CLOSTRIDIUM DIFFICILE - ADJUDICATION FORM

Committee Member: ☐ DJC ☐ ED ☐ JD ☒ JJ

Timing of outcome: (Check all that apply)
- ☐ Pre-PROSPECT randomization
- ☐ Post-PROSPECT randomization, in ICU
- ☐ Post-PROSPECT randomization, post ICU

1. Please provide date of corresponding POSITIVE *Clostridium difficile* microbiological testing: Date (dd/mm/yyyy) 2 0 1

2. Which test was the *Clostridium difficile* based upon (Please check ALL that apply)?
- ☐ ELISA (enzyme-linked immunosorbent assay)
- ☐ PCR (polymerase chain reaction)
- ☐ Cell Culture Cytotoxicity Assay
- ☐ LAMP (loop-mediated isothermal amplification)
- ☐ Other, specify: _____

3. *Clostridium difficile* infection? ☐ No ☐ Yes, specify:
- ☐ ≥ 3 episodes of unformed stools in ≤24 hours
- **AND** ☐ rectal tube in place (hard to quantify)
- ☐ *Clostridium difficile* toxin positive stool
- **OR** ☐ Colonscopic findings demonstrating pseudomembranous colitis
- **OR** ☐ Histopathological findings of pseudomembranous colitis
- **OR** ☐ Diagnosis of toxic megacolon

4. Were any of the following present?

	No	Yes		If present, in the Adjudicators Opinion is this likely attributable *C. Diff* Infection? No	Yes
ICU admission for this reason	☐	☐	→	☐	☐
Mental status changes	☐	☐	→	☐	☐
Fever >38.5°C	☐	☐	→	☐	☐
WBC ≥35.0 or <2.0 x 10^9/L	☐	☐	→	☐	☐
Lactate > 2.2 mmol/L	☐	☐	→	☐	☐
Septic shock (hypotension with vasopressors)	☐	☐	→	☐	☐
Ileus or significant abdominal distention	☐	☐	→	☐	☐
Toxic megacolon	☐	☐	→	☐	☐
Bowel perforation	☐	☐	→	☐	☐
End organ failure (i.e., new mechanical ventilation, dialysis)	☐	☐	→	☐	☐

5. Laboratory (If not available on day of event, record worst value 48 hours pre to 48 hours post event):

Results required only if positive for *C. difficile*

Highest WBC count 10^9/L on day of event ____.____

Highest lactate (mmol/L) on day of event ____.____

Lowest serum albumin (g/L) on day of event ____

Baseline creatinine (umol/L) ____

Highest creatinine (umol/L) on day of event ____

6. *Clostridium difficile* Infection Severity Classification, in the Adjudicators Opinion (Check one ONLY)

☐ Not *C diff* infection ☐ Mild to Moderate ☐ Severe ☐ Severe with complication (see list, questions 4 and 5)

And, if applicable indicate: (Check one ONLY)

☐ Recurrence (within 8 weeks of last *C diff episode* providing symptoms resolved after treatment)

☐ Relapse (same proven strain)

PROSPECT Main RCT 076 Plate #367

Study Day

Patient ID 1

Patient Initials

Date of Study Day (dd/mm/yyyy) 201

CLOSTRIDIUM DIFFICILE - ADJUDICATION FORM

Committee Member: ☐ DJC ☐ ED ☐ JD ☒ JJ

7. Treatment (ever for this event)

- ☐ Antibiotic therapy started, specify ▸
  - ☐ metronidazole — PO ☐ IV ☐ enema ☐
  - ☐ vancomycin — PO ☐ IV ☐
  - ☐ fidaxomicin — PO ☐
- ☐ NONE ☐ N/A
- ☐ Other, specify: _____
- ☐ Fecal transplant
- ☐ Colectomy
- ☐ Randomized CDI treatment trial, specify: _____

8. Clostridium difficile Infection Severity (Check ALL that apply): ☐ N/A NOT a *C. Difficile* Infection

	SHEA	ACG	ESCMID
Mild - Moderate	☐ **SHEA - Mild to Moderate** (check all that apply): ☐ WBC ≤ $15x10^9$/L **AND** ☐ Creatinine < 1.5 X premorbid level	☐ **ACG - Mild to Moderate** (check all that apply): ☐ Diarrhea **PLUS** signs and symptoms **NOT** meeting the criteria for severe or complicated	☐ **ESCMID - Mild to Moderate** (check all that apply): ☐ A clinical picture compatible with CDI and microbological evidence of free toxins and the presence of *C. Diff* in stool without reasonable evidence of another cause of diarrhea **OR** ☐ Pseudommembraneous colitis as diagnosed during endo-scopy, after collectomy or on autopsy
Severe	☐ **SHEA - Severe** (check all that apply): ☐ WBC ≥ $15x10^9$/L **OR** ☐ Creatinine ≥ 1.5 X premorbid level	☐ **ACG- Severe** (check all that apply): ☐ Serum albumin <30g/L **PLUS one of the following:** ☐ WBC ≥ $15x10^9$/L ☐ Abdominal tenderness	☐ **ESCMID - Severe** (check all that apply): ☐ An episode of CDI with **(one or more specific signs and symptoms of)** severe colitis [see table] or a complicated course of disease with significant systemic toxin effects and shock, resulting in the need for ICU admission, colectomy or death
Severe with Complication	☐ **SHEA - Severe with complication** (check all that apply): ☐ Hypotension ☐ Shock ☐ Ileus ☐ Megacolon	☐ **ACG - Severe with complication** (check all that apply): **Any of the following attributable to CDI:** ☐ Hypotension with vasopressors ☐ Fever ≥ 38.5°C ☐ Ileus or significant abdominal distention ☐ Mental status changes ☐ WBC ≥ $35x10^9$/L or <$2x10^9$/L ☐ Lactate > 2.2 mmol/L ☐ End-organ failure (i.e., new mechanical ventilation, dialysis)	

9. Comments:

CHARACTERISTICS OF SEVERE COLITIS

Patient Characteristics that could reasonably be assumed to correlate positively with severity of colitis in the absense of another explantion for these findings:

Category	Signs/symptoms
Physical examination	Fever (core body temperature >38.5°C). Rigors (uncontrollable shaking and a feeling of cold followed by a rise in body temperature). Haemodynamic instability including signs of distributive shock. Respiratory failure requiring mechanical ventilation. Signs and symptoms of peritonitis. Signs and symptoms of colonic ileus. Admixture of blood with stools is rare in *Clostridium difficile* infection (CDI) and the correlation with severity of disease is uncertain.
Laboratory investigations	Marked leucocytosis (leucocyte count >15 × 10^9/L). Marked left shift (band neutrophils >20% of leucocytes). Rise in serum creatinine (>50% above the baseline). Elevated serum lactate (≥5 mM). Markedly reduced serum albumin (<30 g/L).
Colonoscopy or sigmoidoscopy	Pseudomembranous colitis. There is insufficient knowledge on the correlation of endoscopic findings compatible with CDI, such as oedema, erythema, friability and ulceration, and the severity of disease.
Imaging	Distension of large intestine (>6 cm in transverse width of colon). Colonic wall thickening including low-attenuation mural thickening. Pericolonic fat stranding. Ascites not explained by other causes. The correlation of haustral or mucosal thickening, including thumbprinting, pseudopolyps and plaques, with severity of disease is unclear.

PROSPECT Main RCT 076 Plate #368

Study Day

Patient ID 1

Patient Initials

Date of Study Day (dd/mm/yyyy) 2 0 1

CLOSTRIDIUM DIFFICILE - CONSENSUS FORM

Timing of outcome: (Check all that apply)
- ☐ Pre-PROSPECT randomization
- ☐ Post-PROSPECT randomization, in ICU
- ☐ Post-PROSPECT randomization, post ICU

1. Please provide date of corresponding POSITIVE *Clostridium difficile* microbiological testing: Date (dd/mm/yyyy) 2 0 1

2. Which test was the *Clostridium difficile* based upon (Please check ALL that apply)?
- ☐ ELISA (enzyme-linked immunosorbent assay)
- ☐ PCR (polymerase chain reaction)
- ☐ Cell Culture Cytotoxicity Assay
- ☐ LAMP (loop-mediated isothermal amplification)
- ☐ Other, specify: _____

3. *Clostridium difficile* infection? ☐ No ☐ Yes, specify:
- ☐ ≥ 3 episodes of unformed stools in ≤24 hours
- **AND** ☐ rectal tube in place (hard to quantify)
- ☐ *Clostridium difficile* toxin positive stool
- **OR** ☐ Colonscopic findings demonstrating pseudomembranous colitis
- **OR** ☐ Histopathological findings of pseudomembranous colitis
- **OR** ☐ Diagnosis of toxic megacolon

4. Were any of the following present?

	No	Yes	If present, in the Adjudicators Opinion is this likely attributable *C. Diff* Infection? No	Yes
ICU admission for this reason	☐	☐ →	☐	☐
Mental status changes	☐	☐ →	☐	☐
Fever >38.5°C	☐	☐ →	☐	☐
WBC ≥35.0 or <2.0 x 10^9/L	☐	☐ →	☐	☐
Lactate > 2.2 mmol/L	☐	☐ →	☐	☐
Septic shock (hypotension with vasopressors)	☐	☐ →	☐	☐
Ileus or significant abdominal distention	☐	☐ →	☐	☐
Toxic megacolon	☐	☐ →	☐	☐
Bowel perforation	☐	☐ →	☐	☐
End organ failure (i.e., new mechanical ventilation, dialysis)	☐	☐ →	☐	☐

5. Laboratory (If not available on day of event, record worst value 48 hours pre to 48 hours post event):

Results required only if positive for *C. difficile*

Highest WBC count 10^9/L on day of event ____.____

Highest lactate (mmol/L) on day of event ____.____

Lowest serum albumin (g/L) on day of event ____

Baseline creatinine (umol/L) ____

Highest creatinine (umol/L) on day of event ____

6. *Clostridium difficile* Infection Severity Classification, in the Adjudicators Opinion (Check one ONLY)
- ☐ Not *C diff* infection
- ☐ Mild to Moderate
- ☐ Severe
- ☐ Severe with complication (see list, questions 4 and 5)

And, if applicable indicate: (Check one ONLY)
- ☐ Recurrence (within 8 weeks of last *C diff episode* providing symptoms resolved after treatment)
- ☐ Relapse (same proven strain)

PROSPECT Main RCT 076 Plate #369

Study Day

Patient ID 1

Patient Initials

Date of Study Day (dd/mm/yyyy) 2 0 1

CLOSTRIDIUM DIFFICILE - CONSENSUS FORM

7. **Treatment** (ever for this event)

- ☐ Antibiotic therapy started, specify → ☐ metronidazole ☐ vancomycin ☐ fidaxomicin — PO ☐ ☐ — IV enema ☐ ☐ — ☐ NONE ☐ N/A ☐ Other, specify: _____
- ☐ Fecal transplant
- ☐ Colectomy
- ☐ Randomized CDI treatment trial, specify: _____

8. **Clostridium difficile Infection Severity (Check ALL that apply):** ☐ N/A NOT a *C. Difficile* Infection

	SHEA	ACG	ESCMID
Mild - Moderate	☐ **SHEA - Mild to Moderate** (check all that apply): ☐ WBC ≤ $15x10^9$/L **AND** ☐ Creatinine < 1.5 X premorbid level	☐ **ACG - Mild to Moderate** (check all that apply): ☐ Diarrhea **PLUS** signs and symptoms **NOT** meeting the criteria for severe or complicated	☐ **ESCMID - Mild to Moderate** (check all that apply): ☐ A clinical picture compatible with CDI and microbological evidence of free toxins and the presence of *C. Diff* in stool without reasonable evidence of another cause of diarrhea **OR** ☐ Pseudommembraneous colitis as diagnosed during endo-scopy, after collectomy or on autopsy
Severe	☐ **SHEA - Severe** (check all that apply): ☐ WBC ≥ $15x10^9$/L **OR** ☐ Creatinine ≥ 1.5 X premorbid level	☐ **ACG- Severe** (check all that apply): ☐ Serum albumin <30g/L **PLUS one of the following:** ☐ WBC ≥ $15x10^9$/L ☐ Abdominal tenderness	☐ **ESCMID - Severe** (check all that apply): ☐ An episode of CDI with **(one or more specific signs and symptoms of)** severe colitis [see table] or a complicated course of disease with significant systemic toxin effects and shock, resulting in the need for ICU admission, colectomy or death
Severe with Complication	☐ **SHEA - Severe with complication** (check all that apply): ☐ Hypotension ☐ Shock ☐ Ileus ☐ Megacolon	☐ **ACG - Severe with complication** (check all that apply): **Any of the following attributable to CDI:** ☐ Hypotension with vasopressors ☐ Fever ≥ 38.5°C ☐ Ileus or significant abdominal distention ☐ Mental status changes ☐ WBC ≥ $35x10^9$/L or <$2x10^9$/L ☐ Lactate > 2.2 mmol/L ☐ End-organ failure (i.e., new mechanical ventilation, dialysis)	

9. **Comments:** _____

Chapter 6 - Conclusions

6.1 Background

This doctoral thesis focuses on diarrhea, bowel protocols and CDI in critically ill patients, which are relatively under-investigated topics in critical care medicine (Table 1). The data presented herein describe the epidemiology of diarrhea and CDI, demonstrating the incidence, prevalence, and outcomes. Evidence on the prevalence of bowel protocols used in a sample of ICUs is also presented, which may precipitate or perpetuate diarrhea or lead to CDI testing.

6.2 Diarrhea during Critical Illness

Chapter 2 describes the methodology for the DICE-ICU study, and chapter 3 outlines the results of this multicenter observational study of diarrhea in the critically ill. This 1109 patient study showed that diarrhea was common, varied based on the definitions applied, and risk factors are potentially modifiable.

The strengths of this study include the large sample size and its multinational sample enhancing the generalizability of the results. The full protocol and statistical analysis were transparently published in a peer review journal. However, the limitations include possible observer bias, possible uncontrolled confounding, and the lack of mechanistic data.

The next step in this research program will be to design an interventional study to decrease the incidence of diarrhea, a nested observational study to evaluate microbiome alterations in the setting of diarrhea, and generation of a definition of diarrhea that can easily and consistently be applied at the bedside.

6.4 Challenges in studying diarrhea during critical illness

Conducting studies of gastrointestinal dysfunction, specifically diarrhea, during critical illness has several methodological challenges. Compared to other physiologic dysregulation that occurs in critical illness, diarrhea and gastrointestinal dysfunction has been under investigated, leading to many scientific problems.

Defining what constitutes diarrhea in this population is a challenge, as clinicians often do not know of pre-existing bowel habits of their patients, therefore, determining a deviation from a patient's norm difficult. There is also a dearth of research of how the gastrointestinal system alters and adapts during critical illness from clinical symptoms, pathophysiologic changes and how this integrates into a patient's presentation. Highlighting the need to not only address the clinical research gap of diarrhea as well as gastrointestinal dysfunction of this population but also bridge the gap in basic science research of mechanisms.

The other challenge is the lack of an accepted universal definition of diarrhea in the critically ill, as presented in chapter 1 and chapter 2. Without a gold standard definition of diarrhea, conflicting results have been observed on the frequency and the impact of diarrhea in this patient population. For DICE-ICU we chose a definition of diarrhea, the WHO definition, that encompassed frequency and consistency. To ensure that this definition was applied consistently at the bedside, in-services were held with bedside nurses to overcome this barrier.

In future studies of diarrhea, a consistent definition should be implemented to allow better characterization and determination of the true impact of diarrhea on patient important outcomes and facilitate meta-analysis of results.

6.5 Implications of the use of bowel protocols in the ICU

In chapter 4 the results of a content analyses of bowel protocols in 44 ICUs are presented. The study showed that most ICUs have a bowel protocol, and these protocols varied in terms of initiation criteria, medications, escalation, and discontinuation criteria. However, rarely did the protocols include stool assessment which would be ideal to guide the activation and discontinuation of these protocols in practice.

The strengths of this analysis include the broad cross section of ICUs encompassing both community and academic centers. The analysis also included robust characterizations of bowel protocols from implementation of protocols, pharmacotherapy, and contraindications. However, limitations of this study include a selection bias in that included centers were engaged in a randomized trial of probiotics in the critically ill. This study did not explore how institutional protocols were developed or implemented at the bedside.

The next step in this research program is to develop an evidenced based bowel protocol with multidisciplinary input using medications studied in the critically ill, with refined initiation, escalation and discontinuation criteria, incorporating the diarrhea definition used in DICE-ICU, compared to usual care, assessing the impact of the use of the bowel protocol on patient important outcomes. This will be explored first in a pilot

trial to determine feasibility, followed by a large RCT to determine the efficacy of the protocol.

6.6 Challenges in examining bowel protocols in the ICU

As highlighted in chapter 4, the variability in bowel protocols in the ICU is high. There are multiple challenges in developing and researching bowel protocols. Firstly, the protocols need to not only contain medications, but also instructions on how to implement them (e.g., when, how, who etc). Secondly, instructions need to be clearly actionable by bedside nurses to ensure that the protocol is used appropriately and safely. Thirdly, the protocols would ideally be based on evidence (physiologic rationale, or clinical research); however, very few studies have examined the efficacy of a small number of medications in the critically ill. Lastly, studying a bowel protocol as a multifaceted intervention is challenging because there are so many components, not all of which are used in each patient. That is, the way these protocols are used algorithmically means that when they are initiated, not all nodes or directives are activated; this complexity makes it challenging to evaluate bowel protocols in the real-world setting.

6.7 CDI in the critically ill

Chapter 5 contains the results of an observational cohort study of CDI in ICU patients nested within a clinical trial examining the timing, severity, and treatment for CDI. This study demonstrated that CDI is relatively uncommon in the ICU, and if acquired during critical illness, CDI is mild to moderate in severity.

This study had several strengths including a prospectively enrolled population and rigorous methodology including blinded adjudications and the use of three definitions of CDI severity. However, participants in this study were enrolled in a randomized trial requiring them to be mechanically ventilated, which may limit the generalizability of the results. Given the small number of patients with CDI in the cohort, further analyses of CDI risk factors could not be explored.

The next step in this research program will include development of a CDI ICU-specific scoring system and a prospective cohort study to better examine risk factors for CDI in the critically ill patient population.

6.8 Challenges in investigating CDI in the critically ill

As summarized in chapter 5, studying CDI in the ICU has many challenges. For example, prior CDI studies have either used solely microbiological definitions or definitions with minimal clinical data, as following the daily clinical data can be labour intensive and costly. During this study of CDI, new and expanded methods for microbiological confirmation for CDI were developed (e.g. toxinogenic culture, cell cytotoxicity neutralization assay, toxin A/B, nucleic acid amplification tests), which may or may not influence studies describing the prevalence and incidence of this infection. Also, clinical practice guidelines changed twice for treatment, which may influence reported recurrence rates and severity assessments.

Determining the severity of CDI in the critically ill is difficult, as many markers of CDI disease severity are inherent to the population itself. It would be impossible to

judge true CDI severity without the context of the patients' clinical course, such that detailed clinical data and adjudication are needed.

6.9 Future directions

The studies comprising this doctoral thesis have provided the foundation for future work, as outlined in earlier sections. A more intermediate step at the nexus of critical care and gastroenterology clinical research is the future conduct of a large RCT testing the continuous versus bolus delivery of enteral nutrition in the critically ill and its impact on diarrhea and feeding tolerance in this patient population. Embedded in this trial will be a descriptive translational study examining the microbiota in the critically ill, to better characterize the dysbiosis that occurs in patients who develop diarrhea compared to those who do not develop diarrhea.

Table 1: Overview of chapters and included studies

Chapter	Population/Centers	Objective	Methodology	Status of Manuscript
Chapter 1 Introduction	N/A	N/A	N/A	N/A
Chapter 2 DICE-ICU Protocol Paper	Critically ill adults 18 years of age and older admitted to ICU for greater than 24 hours	The objectives of this study were to determine the incidence and frequency of diarrhea, risk factors for diarrhea and consequences (ICU and hospital mortality, ICU and hospital length of stay) of diarrhea in critically ill adults and validate different stool classification systems.	Prospective Cohort Study Protocol	Published in BMJ Open
Chapter 3 DICE-ICU Results Paper	1109 critically ill adults 18 years of age and older admitted to ICU for greater than 24 hours in 12 centers (8 centers in Canada, 2 in the US, 1 in Poland, and 1 in Saudi Arabia).	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 risk factors,	Prospective Cohort Study Results Report	Submitted

		and to describe the management modifications, consequences, and clinical outcomes associated with diarrhea		
Chapter 4 Bowel Protocols in the Critically Ill	44 Centers in Canada, US and Saudi Arabia	The objective of this study was to characterize the content of bowel protocols for the prevention of constipation implemented in ICUs in centers that participated in a randomized trial examining the effects of probiotics for critically ill patients to prevent ICU-acquired infections [Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial (PROSPECT) NCT02462590]. Our secondary objective was to characterize: 1) initiation criteria; 2) medications incorporated; 3) approaches to protocol escalation; 4) discontinuation criteria; 5) stool assessment methods; and 6) contraindications.	Content Analysis of Hospital Documents	Published in the Journal of Critical Care
Chapter 5 *Clostridioides difficle* infection in	86 mechanically ventilated patients with CDI among 2650 critically ill patients in 44	The objectives of this study were to 1) analyze the incidence and prevalence of CDI in the ICU, 2)	Nested Prospective Cohort Study	Soon to be Submitted

Mechanically Ventilated Critically Ill Patients	centers in Canada, the US and Saudi Arabia	describe the timing of CDI infection (pre-ICU, in ICU, and post-ICU), 3) assess the severity of CDI infection using 3 scoring systems and the agreement among scores, 4) document CDI treatments used and 5) examine the outcomes of patients with compared to without CDI.		
Chapter 5 Conclusion	N/A	N/A	N/A	N/A