

AWARD NUMBER: W81XWH-19-1-0287

TITLE: Prebiotic Inulin to Limit Antimicrobial-Resistant Infections During Critical Illness: A Phase II Clinical Trial

PRINCIPAL INVESTIGATOR: Dr. Daniel Freedberg

CONTRACTING ORGANIZATION: Columbia University, New York, NY

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14. ABSTRACT Antibiotic resistance is an emerging healthcare crisis and critically ill patients are among the hardest hit; over half of all infections in intensive care unit (ICU) patients are due to multi-drug resistant (MDR) bacteria, and systemic infection with these bacteria significantly increases risk of death. Active duty military personnel are particularly susceptible to acquisition of MDR organisms due to traumatic injury and because they work in regions where the prevalence of antimicrobial resistance is high. The normal commensal gut bacteria protect against MDR organism (MDRO) colonization, but these protective bacteria are typically lost in the ICU as a result of antibiotics and other interventions. The proposed research hypothesizes that treatments aimed at preserving the gut bacteria that ferment fiber into short-chain fatty acids (SCFAs) will limit the proliferation of antimicrobial resistance within the gut bacteria and ultimately prevent infections with MDROs. Specifically, we will test inulin, a prebiotic fiber made from root vegetables that is the preferred nutrient source for SCFA-producing bacteria. 90 ICU patients will be randomized 1:1:1 to receive placebo or one of two inulin doses for 7 days. The overall aims of the trial are to assess the safety and feasibility of inulin administration in the ICU patients, and its ability to limit the proliferation of antibiotic resistant MDROs.					
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1. Introduction

Antibiotic resistance is an emerging healthcare crisis and critically ill patients are among the hardest hit; over half of all infections in intensive care unit (ICU) patients are due to multi-drug resistant (MDR) bacteria, and systemic infection with these bacteria significantly increases risk for death. Active duty military personnel are particularly susceptible to acquisition of MDR organisms due to traumatic injury and because they work in regions where the prevalence of antimicrobial resistance is high. The normal commensal gut bacteria protect against MDR organism (MDRO) colonization, but these protective bacteria are typically lost in the ICU as a result of antibiotics and other interventions. The proposed research hypothesizes that treatments aimed at preserving the gut bacteria that ferment fiber into short-chain fatty acids (SCFAs) will limit the proliferation of gut antimicrobial resistance and ultimately prevent infections with MDROs. Specifically, we will test inulin, a prebiotic fiber made from root vegetables that is the preferred nutrient source for SCFA-producing bacteria. 90 adult ICU patients with sepsis will be randomized 1:1:1 to receive placebo or one of two inulin doses for 7 days. The overall aims of the trial are to assess the safety and feasibility of inulin administration in the ICU patients, and its ability to limit the proliferation of antibiotic resistant MDROs.

2. Keywords

antimicrobial resistance, antibiotics, intensive care unit, critical illness, sepsis, prebiotics, inulin, fiber, microbiome, colonization, infection, infection control

3. Accomplishments: Year 2 Quarter 1 (end March 2020)

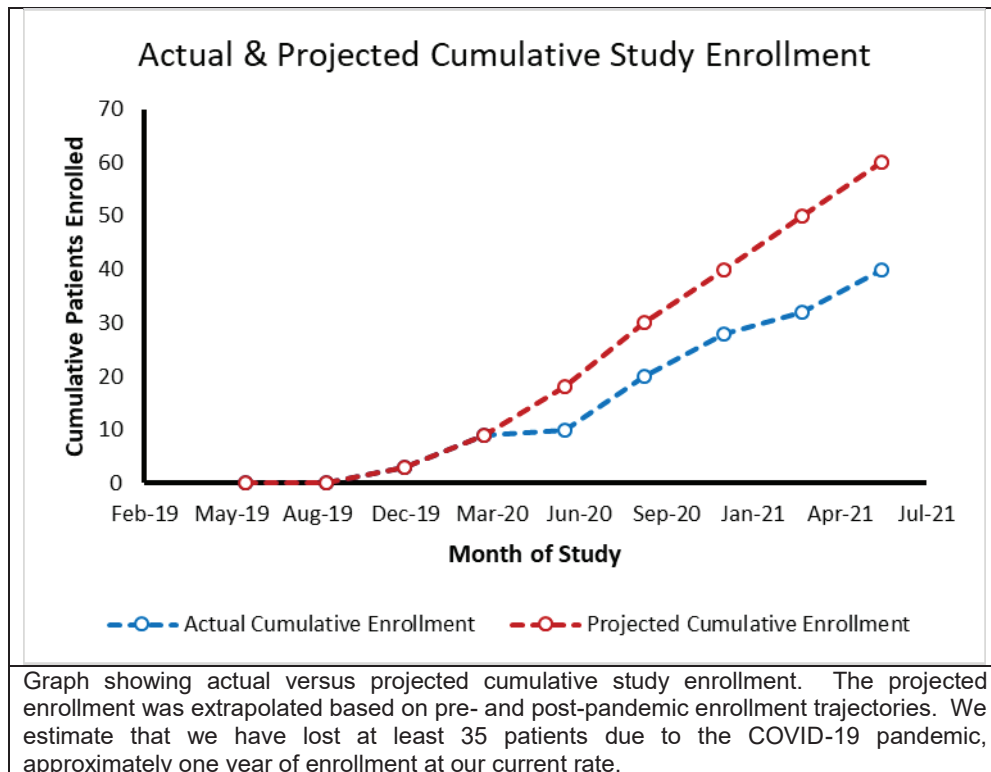
3.1 Major goals

The primary overall goal during this project quarter (ending in funding month 24) was to continue enrolling patients, with a goal of 60 patients enrolled. We did not meet this goal, with 45 subjects enrolled to date (see enrollment timeline below).

Analysis of enrollment shortfall

The shortfall in enrollment is due to the COVID-19 pandemic. Prior to the COVID-19 pandemic, the study was meeting or exceeding enrollment expectations. Our original Statement of Work called for 10 subjects to be enrolled by study month 9, which we accomplished. The pace of enrollment was accelerating when the pandemic began in New York City in the spring of 2020. While the study did continue to enroll during this period, the denominator of eligible patients was fivefold reduced and our enrollment suffered accordingly. Frustratingly, when the pace of enrollment began to pick up during August-September 2020, the COVID-19 “second wave” hit and again slowed us down. During the twelve months from April 2020 to March 2021, we enrolled only 19 patients. Comparatively, during the past three months, we enrolled 9 patients (meaning that we are currently enrolling at a rate of 36 patients per year during the post-pandemic period).

We estimate that we have lost one year of enrollment due to the pandemic, including the time lost due to the protocol changes necessary to accommodate for COVID-19. The graph below depicts the actual and projected number of patients enrolled:



Proposed changes are shown in section 3.2.2.

3.2. Accomplishments under these goals

3.2.1. Major activities

Major study activities during the period from July 1, 2020 to June 30, 2021 are bulleted below.

Regulatory activities

- There were no significant regulatory changes made during this year.

Personnel, hiring, and on-boarding

- There were no changes made to the key study personnel.

Study intervention and supplies

- There were no changes in the study intervention.
- Study supplies continue to be ordered as needed and include but are not limited to: simple cherry syrup, an anti-static weighing canoe, sample collection tubes and bags, distilled water, amber plastic bottles with caps, pipettes, Copan FLOQ swabs, and sterile foam tipped applicators. For the microbiome core lab, Anne-Catrin Uhlemann continues to obtain culture plates for *C. Difficile*, MRSA, VRE, and culture media for Gram negatives including ESBL agar as needed.
- On August 20, 2020, and on February 18, 2021, Elissa Lynch reordered the inulin from Swanson Health as per protocol which dictates the inulin supply be replaced every 6 months. The inulin was shipped from Swanson Health and delivered directly to the CUIMC Research Pharmacy c/o Connie Eng, PharmD.

Study protocol and logistics

- There were no major logistical changes.
- We continue to utilize an E-consent form is captured within the REDCap database and a PDF version is included in the appendices of this report. The IRB approved the E-Consent form and process on June 19, 2020.
- Elissa Lynch continues to meet regularly with the nursing staff on all active study units to discuss study logistics and answer any questions.

Protocol implementation

- The Columbia IRB was revised on February 24, 2020 to broaden the enrollment time constraints. Only when the COVID outbreak subsided in our ICUs in the late summer were we able to utilize this broader time window for the first time, and it greatly improved our denominator of eligible patients. The COVID resurgence in winter temporarily stalled progress. With the ebbing of the pandemic we have seen a sustained increase in our pool of eligible patients and expect to accelerate our enrollment numbers as the year goes on.
- One June 25, 2021, we enrolled on 43rd patient who provided us with Day 3 samples. As of June 30, 2021, we have enrolled 48% of our targeted 90 patients.
- Since the start of the study, 45 out of 120 (38%) patients or surrogates approached for the study have been enrolled.
- The following table cumulatively lists the patients screened for the study.

Patients screened for the study	Number of patients
Screened out	
Does not meet sepsis criteria	132
Unable to receive oral or enteric fluids	84
Known inulin or chicory allergy	0

Hyponatremia with a serum sodium $\leq$ 128	12
Immunosuppressed	15
Intestinal surgery within the last 30 days	4
Limited treatment goals or DNR/DNI	41
Lacks capacity or no available surrogate to consent	31
Total screened out	318
Screened in	
Screened in but declined	75
Screened in but treatment team declined	20
Screened in and enrolled	45
Screened in and donated Day 3 samples	43
Total screened in	140
Grand total screened (in and out)	458

- An enrollment table is shown below (3.2.2, adherence) for the first 45 patients enrolled.

3.2.2. Specific objectives

The primary goal of the study during this phase remains enrollment. We have revised the SOW to replace the time that was lost due to the COVID-19 pandemic. The revised and original Statement of Work would be as follows:

	Revised SOW Timeline (months)	Original SOW Timeline (months)
Major Task 1: Finalize Protocols and Approvals for the Study		
<i>Task goal: regulatory and safety compliance is finalized, study is in the "on deck" position</i>		
No revisions necessary.	Completed	3
Milestone Achieved: Local IRB approval at CUMC, data and safety review with revisions implemented, and HRPO approval for all protocols		
Major Task 2: Coordinate Study Staff for Clinical Trials		
<i>Task goal: concurrent with major task 1, hiring of necessary personnel to implement study, finalization of study protocols</i>		
No revisions necessary.	Completed	8
Milestone Achieved: Trained personnel and independent evaluators throughout the trial		
Major Task 3: Participant Recruitment, Therapy, Participant Evaluation		
<i>Task goal: Initiate Phase 2 Trial</i>		
First participant enrolled	Completed	7-12
Milestone Achieved: 1st participant consented, screened and enrolled, study begins		
N=10 subjects completed Day 7 assessment	Completed	9
N=30 subjects completed Day 7 assessment	Completed	12
N=60 subjects completed Day 7 assessment	33	21
N=90 subjects completed Day 7 assessment	42	30
Milestone Achieved: enrollment for the trial is complete		

Complete 3-month telephone follow-up assessment	45	33
Complete 6-month telephone follow-up assessment	48	36
Milestone Achieved: report crude 6-month follow-up data		

Study adherence

We remain pleased with the adherence to the study intervention, which has been excellent, and with our ability to obtain longitudinal data and re-sample patients at multiple timepoints. While most of the study analyses are focused around the short-term effect of inulin, longitudinal samples will allow us to assess the durability of the intervention.

	Enrollment Date	Doses Received	No. Study Assessments	Final Assessment
Patient 1	10/14/19	14	4	Day 14
Patient 2	12/3/19	14	4	Day 14
Patient 3	12/11/19	13	5	Day 30
Patient 4	1/3/20	14	4	Day 14
Patient 5	1/7/20	14	4	Day 14
Patient 6	1/23/20	11	4	Day 14
Patient 7	2/4/20	1	2	Day 3
Patient 8	2/4/20	13	5	Day 30
Patient 9	2/28/20	12	5	Day 30
Patient 10	6/23/20	8	4	Day 14
Patient 11	7/29/20	14	5	Day 30
Patient 12	8/6/20	13	4	Day 14
Patient 13	8/26/20	14	4	Day 14
Patient 14	9/8/20	12	4	Day 14
Patient 15	9/8/20	13	4	Day 14
Patient 16	9/10/20	11	5	Day 30
Patient 17	9/14/20	13	4	Day 14
Patient 18	9/14/20	12	4	Day 14
Patient 19	9/22/20	2	2	Day 3
Patient 20	9/25/20	14	5	Day 30
Patient 21	10/12/20	6	4	Day 14
Patient 22	10/19/20	3	1	Day 0
Patient 23	10/22/20	14	5	Day 30
Patient 24	10/22/20	14	5	Day 30
Patient 25	11/6/20	13	3	Day 7
Patient 26	11/13/20	13	5	Day 30
Patient 27	11/13/20	12	3	Day 7
Patient 28	11/20/20	12	4	Day 14
Patient 29	1/21/21	14	3	Day 7
Patient 30	1/22/21	11	2	Day 3
Patient 31	2/9/21	11	2	Day 3
Patient 32	3/21/21	11	3	Day 7
Patient 33	3/24/21	5	3	Day 3
Patient 34	4/7/21	13	4	Day 14

Patient 35	4/21/21	11	4	Day 14
Patient 36	5/10/21	13	4	Day 14
Patient 37	5/11/21	12	4	Day 14
Patient 38	5/25/21	0	1	Day 0
Patient 39	5/27/21	3	5	Day 30
Patient 40	5/27/21	4	5	Day 30
Patient 41	6/16/21	4	2	Day 3
Patient 42	6/18/21	14	3	Day 7
Patient 43	6/21/21	14	4*	Day 14*
Patient 44	6/23/21	14	4*	Day 14*
Patient 45	6/25/21	14	4*	Day 14*

*Any subsequent assessments obtained will be included in the next quarterly report.

Summary sample data is as follows:

Sample type	Number of samples
Rectal swabs	165
Oral swabs	165
Whole stools	76
Urine	105
Residual blood	60
Total samples	571

3.2.3. Significant results

Trial findings are anticipated in year 4 of the award.

3.2.4. Other achievements

Nothing to report.

3.3. Opportunities for training and professional development

Nothing to report.

3.4. Dissemination of results to communities of interest

The following relevant presentations were given by Dr. Freedberg during this quarter:

1. Local talks only.

3.5. Plans for the next reporting period

The new primary goal for the next reporting period (Y3Q1) is to continue enrolling so that we can meet the revised SOW goal of 60 patients enrolled by month 33 of the study (Y3Q3).

4. Impact

Nothing to report. It is anticipated that the main impact of the trial will be after the final results have been published and disseminated, towards the conclusion of the award.

5. Changes/problems

The revised SOW will necessitate a revision in the budget, with a reallocation of funds to cover a fifth year (i.e., providing for an additional year of enrollment to make up for the time lost due to COVID-19). To briefly summarize, we plan to spread the salaries for Y4 across Y4 and the new Y5. In order to provide for continued RN effort, Drs. Uhlemann and Abrams will take small drops

in effort but they will continue to contribute sufficient effort to perform the work as described. qPCR for resistance genes will begin in Y4 of the award and continue into Y5. Sequencing and other major assays will be done in Y5 of the award instead of Y4 as originally planned. The total cost of the award remains exactly the same. A draft budget reallocation is attached below.

6. Products

It is anticipated that the main products of the trial will be after the trial has been completed, towards the conclusion of the award.

7. Participants and other collaborating organizations

7.1. Individuals who have worked on the project

In addition to the individuals listed below, the following individuals have contributed to the project at less than 1 annualized calendar month of effort: Zhezhen Jin (Co-I, 0.5 Cal Mos), Romina Wahab (Co-I, 0.4 Cal Mos). Dr. Wahab has assumed the place of Dr. Chong, who left the institution.

Name:	Daniel Freedberg
Project role:	PI
Researcher identifier:	ORCID 0000-0003-2023-2899
Nearest person-month worked:	2.4
Contribution to project:	Dr. Freedberg has overseen all of the research activities described in this report and in the original SOW, including all of the study set-up activities that have taken place during this quarter.
Funding support:	Columbia Irving Scholar Award, Columbia-Takeda Pilot Award (Co-I)

Name:	Julian Abrams
Project role:	Co-I
Researcher identifier:	ORCID 0000-0002-6021-9376
Nearest person-month worked:	1.8
Contribution to project:	Dr. Abrams meets with Dr. Freedberg weekly to strategize regarding the study, and helps with study conduct and oversight and with planning of analyses and assays.
Funding support:	R01 CA238433, U54 CA163004

Name:	Anne-Catrin Uhlemann
Project role:	Co-I
Researcher identifier:	ORCID 0000-0002-9798-4768
Nearest person-month worked:	1.2
Contribution to project:	Dr. Uhlemann, who heads Columbia's microbiome core facility, will oversee all of the microbial cultures and analyses described under this award.
Funding support:	R01 AI116939, R35 HL135800, U01 AI131339, R21 HL145319, R01 CA238433, U54 DK104309

Name:	Elissa Lynch
Project role:	Research Nurse
Researcher identifier:	None

Nearest person-month worked:	12
Contribution to project:	RN Lynch works full-time with Dr. Freedberg on the set-up and conduct of the study, gathering of samples and data, and arranging sample assays and analyses.
Funding support:	None.

7.2. Change in active other support for key personnel

No changes.

7.3. Other organizations involved as partners

Nothing to report.

8. Special reporting requirements

The U.S. Army quad chart is included as the first item in the appendices.

ORIGINAL BUDGET

Salary Expenses	Year 4				
Personnel	Role	% Eff	Sal	FB	Total
Freedberg, Daniel	PI	0.2			
Abrams, Julian	Co-I	0.15			
Uhlemann, AC	Co-I	0.08			
Jin, Zhezhen	Biostats	0.04			
Chong, David	Co-I	0.03			
Annavajhala, M. (ACU Lab)	PD	0			
Elissa Lynch	RN	0.75			
Total Salary					
Total Non Salary					
Total DC Y4					

REVISED BUDGET

Salary Expenses	Year 4					Year 5				Total Y4 & Y5
Personnel	Role	% Eff	Sal	FB	Total	% Eff	Sal	FB	Total	
Freedberg, Daniel	PI	0.1				0.1				
Abrams, Julian	Co-I	0.075				0				
Uhlemann, AC	Co-I	0.02				0.02				
Jin, Zhezhen	Biostats	0.04				0.04				
Chong, David	Co-I	0.01				0.01				
Annavajhala, M. (ACU Lab)	PD	0				0.75				
Research Nurse (TBD)	RN	0.5				0.5				
Total Salary										
Non-Salary Expenses										
Sample retrieval and storage										
16S rRNA Gene Sequencing										
Bacterial Culture										
qPCR for 87 Resistance Genes										
Whole Genome Sequencing										
Fecal SCFA Levels										
Data Management										
Total Non Salary										
Total DC Y4 & Y5										

9. Appendices

9.1	U.S. Army Medical Research Acquisition Activity Quad Chart
9.2	Current working version of the study protocol (v5)
9.3	Approved Columbia IRB #AAAS2576 (approval date 3/17/20)
9.4	Approved Columbia consent form (English)
9.5	Approved Columbia consent form (Spanish)
9.6	Approved Columbia E-consent form (REDCap PDF)
9.7	Case Report Forms (print version of a REDCap-based system)
9.8	Current c.v. of Dr. Freedberg (PI)
9.9	Peer-reviewed research published by key study personnel during this reporting period (July 2020-June 2021)
9.10	Columbia IRB Approval Letter

Appendix 9.1

Prebiotic inulin to limit antimicrobial-resistant infections

Contract W81XWH1910287
PR181960



PI: Daniel Freedberg

Org: Columbia University

Award Amount: 1,890,421.00

Study Aims

Aim 1: To determine the feasibility, tolerability, and safety of inulin in the ICU.

Primary outcome: Feasibility, assessed as enrollment rate, protocol adherence, and intervention fidelity.

Aim 2: To determine the impact of inulin on gut colonization with antibiotic-resistant pathogens.

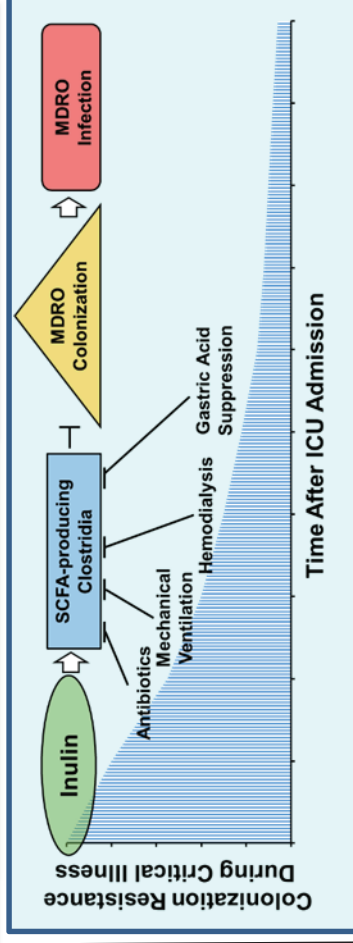
Primary outcome: gut antibiotic resistance colonization status, assessed based on culture from serial rectal swabs.

Aim 2A: To determine the impact of inulin on ICU-acquired antibiotic-resistant infections.

Primary outcome: composite of death and ICU-acquired infections.

Approach

To accomplish these Aims, we will conduct a Phase 2 double-blind clinical trial. ICU adults meeting sepsis criteria will be randomized to receive inulin 32 g/day, inulin 16 g/day, or placebo for 7 days and will donate samples and data on ICU days 0, 3, 7, 14, and 30.



Schematic depicting the scientific rationale for the proposed trial. Gastrointestinal colonization resistance gradually declines during critical illness. Multidrug-resistant organisms (MDROs) colonize the gut and are disseminated into the ICU room, and ultimately inoculated into the patient to cause systemic infection. Inulin, a soluble prebiotic fiber, promotes the growth of short chain fatty acid (SCFA)-producing bacteria which decreases MDRO colonization and downstream infection. Data from healthy volunteers supports the beneficial effects of inulin while data from our own ICU demonstrates the importance of SCFA-producing bacteria in gastrointestinal colonization resistance.

Timeline and Cost

Activities (AY)	Y1	Y2	Y3	Y4	Y5
Aim 1: Feasibility, tolerability, safety					
Aim 2: Colonization					
Aim 2A: Infection					
Budget (k)	\$462	\$443	\$402	\$254	\$329

Updated: July 2021

Goals/Milestones

Y1: AY19-20 Goal – Protocol finalization

☒ Implement protocol and complete enrollment of 30 patients

Y2: AY20-21 Goals – Ongoing enrollment

☒ Enroll 45 patients

Y3: AY21-22 Goal – Ongoing enrollment

☐ Enroll 60 patients

Y4: AY22-23 Goal – Ongoing enrollment and beginning assays

☐ Enroll 90 patients

☐ Lock data and begin assays

Y5: AY23-24 Goal – Assays and data analysis

☐ Finalize and lock trial primary results

☐ Data analysis and dissemination

Comments/Challenges/Issues/Concerns

- No-cost extension requested for loss of enrollment with COVID.

Appendix 9.2

CLINICAL TRIAL PROTOCOL

Prebiotic Inulin to Limit Antimicrobial-Resistant Infections During Critical Illness: A Phase 2 Clinical Trial

Draft Date: February 24, 2020

Version 5

Columbia IRB: AAAS2576
FDA IND: 137359
DoD PRMRP: PR181960
DoD HRPO: Log Number E00684.1a
ClinicalTrials.gov: NCT03865706

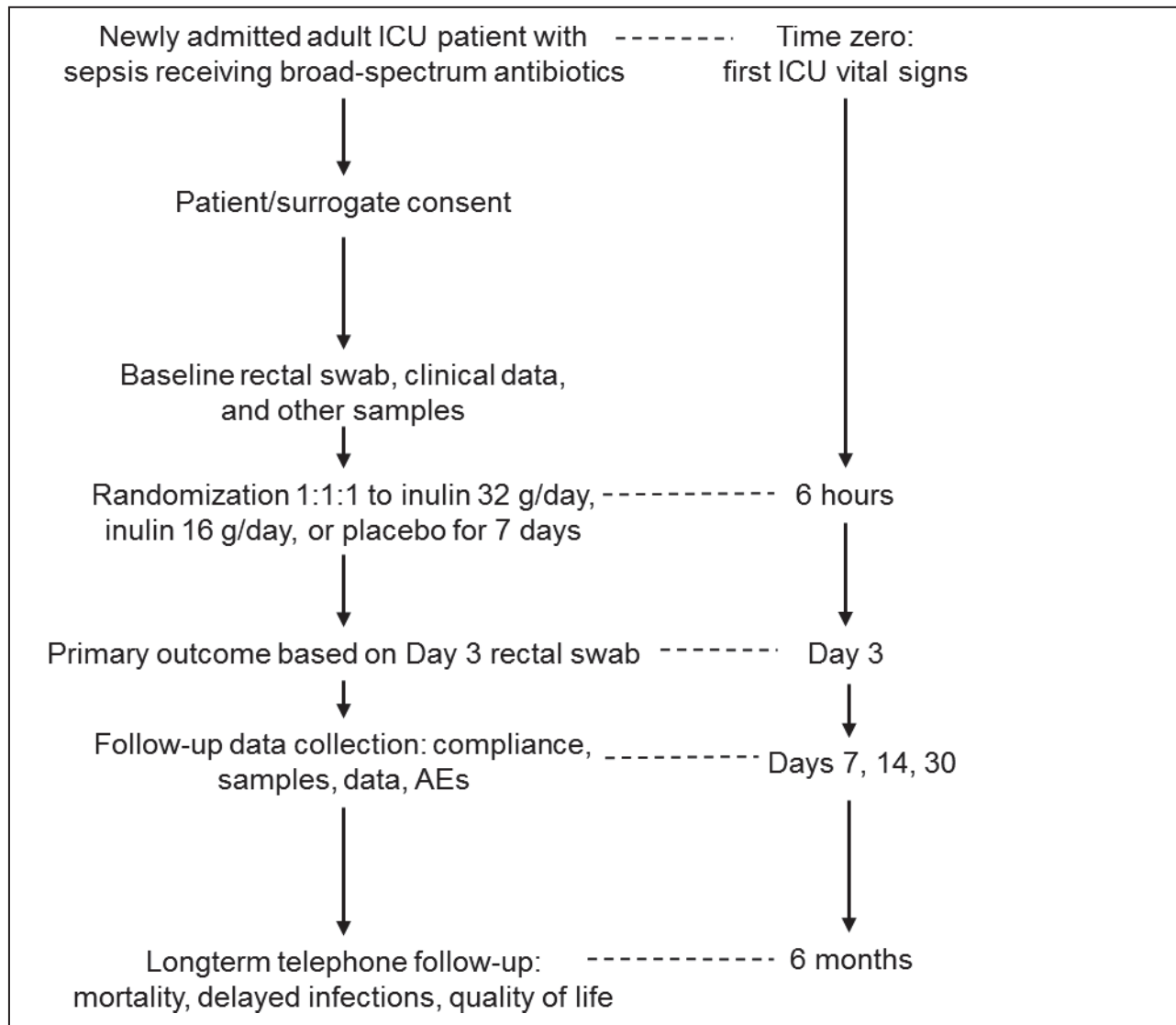
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2. Protocol synopsis

Title	Prebiotic Inulin to Limit Antimicrobial-Resistant Infections During Critical Illness: A Phase 2 Clinical Trial
Short title	Inulin in the ICU
Design	Randomized, double-blind, placebo-controlled trial in the ICU
Outcomes	<i>Primary outcome:</i> Change in relative abundance of SCFA producers through ICU Day 3 <i>Secondary outcome:</i> MDRO colonization status on ICU Day 3 <i>Additional outcomes:</i> 1. Feasibility 2. Rates of pre-specified AEs 3. Antibiotic resistance gene fraction on ICU Day 3 4. Culture-proven MDR infections through ICU Day 30 5. Fecal SCFA levels 6. Proportion of goal calories through ICU Days 3 and 7 7. Length of ICU stay 8. Length of hospital stay 9. Mortality through ICU Day 90 10. Self-assessed quality of life at 6 months 11. Times series data including ICU Day 7 outcomes
Intervention	1:1:1 allocation to inulin 32 g/day, inulin 16 g/day, or placebo dissolved in 250 cc sterile water and given in 2 daily doses for 7 days or until death/hospital discharge
Sample size	90 critically ill patients meeting Sepsis-3 criteria
Eligibility criteria	<i>Inclusion criteria:</i> 1. Medical ICU 2. Age ≥ 18 years old 3. Sepsis, defined according to the Sepsis-3 (2016) consensus as a known or suspected infection with a SOFA score of ≥ 2 points above baseline 4. Broad-spectrum antibiotics, received within the last 24 hours or ordered and pending administration 5. Able to complete enrollment within 24 hours of ICU admission for administration of the intervention within 48 hours of ICU admission <i>Exclusion criteria:</i> 1. Inability to receive oral or enteric fluids 2. Inulin allergy 3. Hyponatremia (serum sodium ≤ 128 mEq/L) 4. Immunosuppression, defined as CD4 count < 200 or absolute neutrophil count < 500 or reasonable expectation of either during the study intervention period 5. Surgery involving the intestinal lumen within 30 days or known intestinal strictures 6. Do Not Resuscitate (DNR) or Do Not Intubate (DNI) status, or “no escalation of care” orders 7. Lack capacity for consent and no appropriate Legally Authorized Representative (LAR).

2.1 Study diagram



3. Administrative information

Primary Investigator	Daniel E. Freedberg def2004@cumc.columbia.edu Columbia University Medical Center Division of Digestive and Liver Diseases 622 West 168 th Street, P&S Building 3-401, New York, NY 10032 Research office: (212) 342-3302, Cell: (857) 998-9370
Co-Investigators	<i>All at Columbia University Medical Center</i> Julian Abrams: ja660@cumc.columbia.edu David Chong: dhc5@cumc.columbia.edu Zhezhen Jin: zj7@columbia.edu Anne-Catrin Uhlemann: au2110@@cumc.columbia.edu
Data and Safety Monitoring Officer	Daniel Brodie hdb5@cumc.columbia.edu Columbia University Medical Center Vivian and Seymour Milstein Family Heart Center 173 Fort Washington Avenue, 4-005A, New York, NY 10032 Phone: (212)305-9817
Other Key Personnel	Howard Andrews, Columbia University Data Coordinating Center, hfa1@columbia.edu Research Nurse to be hired

4. Funding

This project is funded by a Department of Defense Peer-Reviewed Medical Research Program Clinical Trial Award (PR181960) recommended for funding on February 20, 2019.

4.1 Role of funding bodies

The study will be designed and conducted, and the results analyzed, presented, and published by the investigators independent of the funding bodies.

5. Background and rationale for study

5.1 Background

Multidrug resistant (MDR) bacterial infections are a leading cause of morbidity, death, and healthcare-associated costs.¹⁻³ Nowhere is this more important than in the intensive care unit (ICU), where over half of all infections are MDR⁴ and where sepsis from MDR bacteria confers 10-20% absolute increased mortality.⁵⁻⁷

This project hypothesizes that antibiotic resistance in the ICU is a problem of the human gastrointestinal microbiome, which is the critical reservoir for the bacteria and plasmids that encode antibiotic resistance genes.⁸⁻¹⁰ The normal gut microbiota prevents colonization and subsequent infection with MDR organisms through competition for scarce resources and other mechanisms.¹¹ In the setting of critical illness, normal colonization resistance is lost and there are no currently available therapies to restore it.¹²⁻¹⁵

Specific gut bacteria contribute to colonization resistance. ICU patients have low levels of butyrate and other short chain fatty acids (SCFAs) which are derived from dietary fiber by anaerobic bacteria primarily within the Clostridial Clusters IV and XIVa (e.g., *Faecalibacterium prausnitzii*). SCFAs moderate colonic inflammation,¹⁶ enlarge the pool of regulatory T cells,¹⁷ and

contribute to the thickness of the colonic mucus layer and pathogen resistance.¹⁸ During critical illness, levels of SCFA-producing bacteria and SCFAs are low, and these levels further decline with antibiotic treatment. Loss of SCFA-producing bacteria correlates with an increase in colonization with vancomycin-resistant *Enterococcus* and other antibiotic-resistant pathogens. We believe that preservation of SCFA-producing bacteria during critical illness is of major importance and can prevent the proliferation of colonizing organisms with antimicrobial resistance.

The prebiotic fiber **inulin** is a vegetable-derived polysaccharide that restores gastrointestinal colonization resistance against MDROs. SCFAs cannot be easily given to humans due to oral intolerance and rapid metabolism,^{19,20} but inulin promotes growth of SCFA producers to raise SCFA levels. In animals, inulin-type fibers improve survival after pathogen challenge^{21,22} even in the face of antibiotics.^{18,23-25} In a randomized trial of 30 outpatients, inulin increased fecal levels of SCFA producers by 35-90%, with a 3-fold decrease of serum markers of bacterial translocation (e.g., lipopolysaccharide) relative to placebo.²⁶ Inulin is safe in ambulatory patients²⁷⁻³⁵ with biologic effects seen at 16 g/day.²⁶ In the ICU, inulin-type fibers have been given up to 36 g/day without adverse events³⁶ and in our ICU cohort we have observed 30 g/day dietary fiber without intolerance. This trial will test whether inulin supplementation has similar effects in the ICU as it does in animal models and as it appears to in healthy volunteers: will it result in higher levels of SCFA-producing Clostridia, decreased gastrointestinal antibiotic resistance and lower risk for MDR infections?

5.2 Trial purpose and design

The purpose of this Phase 2 trial is to determine the feasibility and safety of inulin for the prevention of antibiotic resistant infections or colonization in critically ill patients. We will perform a double-blind, randomized controlled trial of inulin in the ICU with three arms (placebo, inulin 8 g twice daily, and inulin 16 g twice daily). Subjects will be treated with inulin or placebo for 7 days with bedside follow-up for 30 days or hospital discharge and with long-term telephone follow-up for 6 months.

6. Previous data

Our observational ICU data supports the importance of SCFA producers in the ICU. In animals, inulin protects against sepsis. Inulin increases SCFA producers in ambulatory studies and inulin-like fibers are safe in the ICU setting.

6.1 Evidence supporting the importance of SCFA producers in the ICU

We have assembled two large prospective cohorts now totaling over 500 ICU patients who have contributed rectal swabs and other data.³⁷⁻³⁹ Results from these cohorts confirm the importance of SCFA producers in protecting against pathogen colonization and infection in the ICU.

- **Cohort #1.**⁴⁰ A single rectal swab was performed on medical ICU admission for consecutive patients. Swabs were cultured for VRE and residual DNA was extracted for 16S rRNA gene sequencing; patients were then followed for up to 30 days for death or culture-proven infections. In 9 months, **301 patients** were enrolled of whom 91 (30%) were VRE colonized. Thirty-day mortality was 25% and an overlapping 21% patients developed culture-proven MDR infections.

Cohort #1 demonstrated that the bacteria causing infections in the ICU are present as gut colonizers at the time of admission. We tested whether colonizing MDROs predicted subsequent death or culture-proven infection. Presence of the colonizing organism at ICU admission was almost always associated with subsequent organism-specific infection, even after adjusting for

acute severity illness as captured by the Simplified Acute Physiology Score-3 (SAPS-3)^{41,42} and other relevant clinical variables. This was true for VRE (aHR 5.85, 95% CI 2.25-15.2, 16 infections), *C. difficile* (aHR 19.0, 95% CI 4.40-81.8, 9 infections), *Pseudomonas* (aHR 2.37, 95% CI 1.04-5.43, 28 infections), and *Klebsiella spp.* (aHR 3.81, 95% CI 1.10-13.2, 28 infections). To interrogate the process by which MDRO colonization may lead to infection, we also examined MDRO domination defined as $\geq 30\%$ 16S reads corresponding to a potential pathogen.^{43,44} Because this cohort contained VRE culture data, we were able to test whether patients who had *Enterococcus* domination were in fact colonized by VRE. *Enterococcus* domination (15% of the cohort) and VRE colonization (30%) both

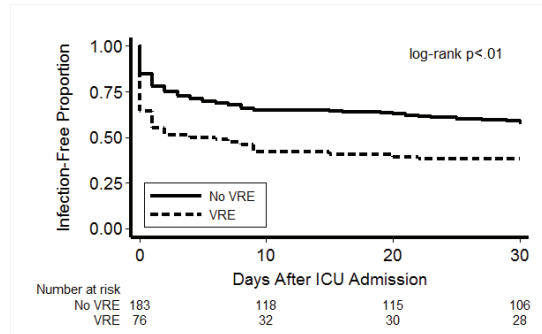


Figure 1. VRE colonization/domination was associated with death or culture-proven infection in the ICU. VRE colonization or domination was assessed at the time of ICU admission and patients were followed for all-cause culture-proven infection.

predicted *all-cause* infection (**Figure 1**). When 30-day mortality was examined as a stand-alone outcome, VRE colonization/domination predicted 40% increased mortality, after adjusting for SAPS-3 score and other factors.

Next, we sought to determine the relationship between SCFA producers and VRE based on culture at the time of ICU admission. Only VRE was cultured within this cohort, so we did not have the ability to assess colonization with other MDROs using culture (e.g., Gram negative bacteria). Based on the 16S sequencing results, SCFA producers were classified as absent (<.01% relative abundance), low (.01% to 1%), or high (>1%) after Haak *et al.*⁴⁵ High levels of SCFA producers were associated with lower prevalence of VRE colonization based on culture: 40% when SCFA producers were absent, 27% when they were low, and 22% when they were high ($p < .01$). Results were similar for *Enterococcus* domination.

- **Cohort #2.**^{37,39} This cohort was designed to examine *dynamic* changes in the ICU microbiome, focusing on SCFA producers and MDROs. Swabs were performed in duplicate at ICU admission and 72 hours later (± 4 hours). Swabs were then (1) cultured for MRSA, VRE, and MDR Gram negatives and (2) 16S sequenced. In 3 years, **230 patients** out of a target of 300 have been enrolled with 126 sequenced to date.

Cohort #2 demonstrated that SCFA-producing bacteria associate with preserved colonization resistance. Within cohort #2, we first performed an unbiased analysis using LEfSe⁴⁶ to ask which bacterial taxa changed most within individuals, comparing their admission and Day 3 samples. 14 taxa were identified as having significantly changed at a false-discovery adjusted $p < .05$. Ten taxa decreased over these first 72 hours of which 6 were SCFA producers. These changes were substantial in magnitude (e.g., 8-fold for *F. prausnitzii*).

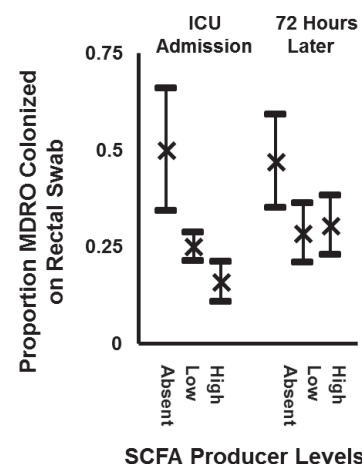


Figure 2. Higher levels of SCFA-producing bacteria associated with lower colonizing MDROs, both at the time of ICU admission and 72 hours later. Lines are 95% confidence estimates.

We wanted to know how SCFA producers associated with MDRO colonization. SCFA producers were again classified as absent, low, or high based on sequencing. MDROs were classified as present vs absent based on culture results. At both ICU admission and 72 hours later, there was a stepwise relationship

where higher SCFA producers was associated with decreased MDRO colonization (**Figure 2**, previous page). Comparing high to absent SCFA levels, the difference in rates of MDRO colonization was over 25%.

Last, we sought to retrospectively assess the impact of dietary fiber on SCFA producers and MDROs. Observed fiber intake was low overall with a mean of 13.4 g over 72 hours, but some patients did receive large amounts of fiber (maximum 30 g/24 hours). There was no intolerance of fiber based on documentation of abdominal distension, diarrhea, or nausea/vomiting. Fiber intake was classified into tertiles and SCFA producers were examined as a continuous measure based on 16S sequencing. At ICU admission, baseline relative abundance of SCFA producers was similar across fiber intake groups. After 72 hours, higher fiber intake was associated with higher levels of SCFA producers (**Figure 3**). Higher fiber was also associated with less *Enterococcus* (median abundance .08% high

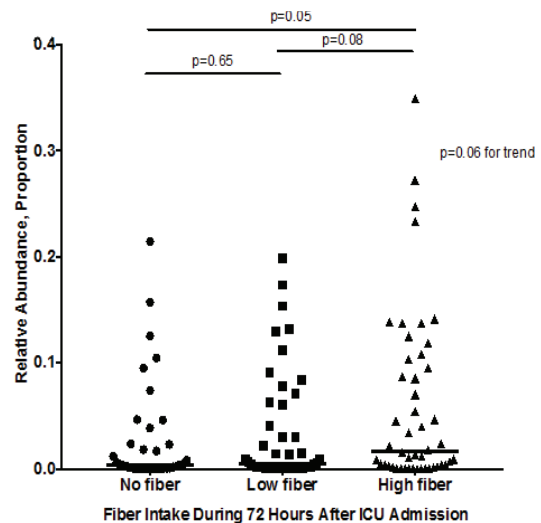


Figure 3. Higher fiber intake associated with higher levels of SCFA producers in the ICU. Fiber intake was classified into tertiles, with relative abundance of SCFA producers classified based on 16S sequencing.

fiber vs .35% no fiber, $p=.03$). This data is observational so there were baseline patient differences between those who did and did not receive high dietary fiber. To account for this, we built a multivariable model adjusted for acute severity of illness, receipt of antibiotics, and total caloric intake. In this model, there was a 0.30% median increase in SCFA producers after 72 hours per additional 10g of fiber intake ($p<0.01$). This suggests that dietary fiber has the potential to impact levels of SCFA producers, even during critical illness and with receipt of broad-spectrum antibiotics (78% of the cohort).

6.2 Inulin in animal models

Animal models show protective effects of inulin or similar compounds, which appear to be mediated by an increase in SCFA producers.^{47,48} Importantly, these studies demonstrate that inulin is likely to be effective even when given concurrently with antibiotics. Animal models include cecal ligation and puncture (CLP),²¹ lipopolysaccharide (LPS) injection,²² challenge with *Citrobacter rodentium*¹⁸ or pathogenic *Escherichia coli* strains,⁴⁷ and *Salmonella typhimurium* challenge with²³ or without antibiotics.^{24,25} All models have their strengths and weaknesses, so it is remarkable that results align well across them. Inulin and similar fructo-oligosaccharides (FOS) seem to confer protective effects through multiple mechanisms all of which likely depend on SCFA fermenters. First, they maintain the protective colonic mucus layer. Inulin fermenters activate carbohydrate metabolism pathways and switch fuel utilization from dietary fiber to colonic mucus when inulin-like fibers are unavailable, causing thinning of the colonic mucus layer.^{18,23} Second, the bacteria nourished by inulin have direct antagonistic effects on pathogens²⁵ by making protonated SCFAs which diffuse across Gram negative cell walls to delay pathogen growth.²⁴ Luminal acidification by SCFAs also drives broad microbiome shifts towards relatively pH-tolerant, Gram positive obligate anaerobes.^{49,50} Third, SCFA producers induce host immunity. When SCFA-producing anaerobe levels increase during sepsis, there is induction of T regulatory cells (Tregs), reduction in activated dendritic cells, and downstream decreased DNA binding of NF- κ B for an overall reduction in pro-inflammatory cytokines and reduced T cell anergy.²² In these animal studies, the protective effect is large, with dramatic differences in outcomes including weight loss, colitis severity, and mortality.

6.3. Inulin in the ambulatory setting

Inulin has been studied in over 400 ambulatory patients where it has shown excellent safety and tolerability.²⁷⁻³⁵ No serious adverse events have been reported in trials using doses up to 34 g/day inulin⁵¹ or 55 g/day mixed fiber,¹⁶ with self-resolving bloating the main side effect. Three trials specifically examined outcomes related to the ability of inulin to prevent colonization or infection. First, Dewulf *et al.* randomized 30 patients to inulin 16 g/day vs placebo; the inulin group had a doubling of *F. prausnitzii* and other SCFA-producers and concurrent decreases in serum CRP and LPS concentration.²⁶ Second, Lecerf *et al.* randomized 60 volunteers 1:1:1 to placebo, a combination xylo-oligosaccharide (XOS), or inulin-XOS.⁵² The inulin group had the highest post-treatment SCFA levels and butyrate levels, the lowest circulating LPS, and decreased gene expression for the pro-inflammatory cytokines IL-1 β , TNF α , and IL-12. Third, Miguez *et al.* found that an inulin-like fructo-oligosaccharides (FOS) preserved gut microbiome diversity after broad-spectrum antibiotics, mitigated loss of SCFA producers, and increased butyrate levels 3-fold.⁵³ **Table 1** lists selected studies of inulin in the ambulatory setting, focusing on those with results most relevant to this project.

Table 1. Selected ambulatory trials testing inulin alone or in combination

Author	Subjects	Intervention	Effect	AEs
Kruse ⁵¹	8 healthy volunteers	Inulin 34 g/day	Increased <i>Bifidobacteria</i> , unchanged SCFA levels	Self-resolving bloating and flatulence.
Dewulf ²⁶	30 obese women	inulin 16 g/day (50% FOS enriched) x 3 months	Increased <i>Bifidobacteria</i> and <i>F. prausnitzii</i> and decreased LPS.	Self-resolving bloating and flatulence.
Lecerf ⁵²	60 healthy volunteers	inulin 3g/day plus 1g/day XOS	Increased fecal SCFAs, decreased LPS, attenuated LPS-induced serum changes in IL-1b and IL-13.	Self-resolving bloating and flatulence, small decrease in general well-being.
Azpiroz ²⁷	36 with IBS	inulin 8g/day x 4 weeks	Increased <i>Bifidobacteria</i> .	None reported.
Canfora ²⁹	44 obese pre-diabetic adults	inulin 15g/day x 12 weeks	Increased <i>Bifidobacteria</i> .	None reported.
Garcia-Peris ³⁰	31 adult women with gynecological cancer	inulin 12g/day x 4 weeks (50% FOS enriched)	Increased in <i>Lactobacillus</i> and <i>Bifidobacteria</i> .	Self-resolving bloating.
Holscher ³¹	29 healthy adults	inulin 7.5g/day x 21 days (agave-derived)	Increased <i>Bifidobacteria</i> .	None reported.
Petry ³²	32 obese female adults	inulin 20 g/day x 4 weeks	Increased <i>Bifidobacteria</i> .	None reported.
Rahat-Rozenbloom ⁵⁴	25 healthy obese or lean adults	inulin 24 g/day x 3 days	Increased serum SCFAs.	None reported.
Ramirez-Farias ³³	12 healthy adults	inulin 10g/day x 16 days	Increased <i>Bifidobacteria</i> and <i>F. prausnitzii</i> , no change in fecal SCFAs.	None reported.
Vandeputte ³⁵	42 healthy adults	inulin 12g/day x 4 weeks	Increased <i>Bifidobacteria</i> .	None reported.

6.4 Inulin-like fibers in the ICU

Inulin has not been studied in the ICU but data can be extrapolated from ICU trials of similar fructo-oligosaccharides (FOS). To date, there are no reports of serious adverse effects or major intolerance with over 1,000 patients studied.⁵⁵ Doses have been used up to 36 g/day for 5 weeks.³⁶ This emerging safety data is robust enough that consideration of supplemental fiber has

been incorporated into relevant ICU nutrition guidelines.⁵⁶ Data on the effects of inulin-like FOS on infections in the ICU is scarce but promising. Three double-blind, randomized ICU trials tested a commercial synbiotic containing *Lactobacillus spp.* and mixed soluble prebiotic fiber including some inulin (up to 20 g/day total).⁵⁷⁻⁵⁹ In these studies, the overall rates of ICU-acquired infections were 16-27% lower in the group receiving prebiotic fiber, although MDR infections were not separately examined. In an open-label trial of mixed fiber up to 24 g/day in 30 critically ill adults, the median hospital length of stay was 5 days shorter in the fiber group and the overall rate of complications, including feeding-related complications was lower.⁶⁰ This provides important reassurance given the concerns occasionally raised regarding prebiotics in patients with altered small bowel or colonic motility.^{61,62} **Table 2** lists selected studies of fiber supplementation in the ICU, focusing on those with results most relevant to this project

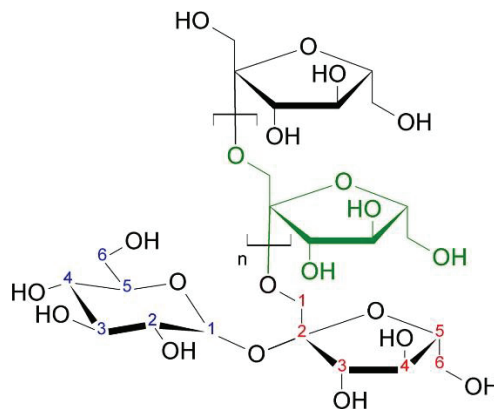


Table 2. Selected ICU-based trials testing inulin or similar fibers, ordered by decreasing amounts of fiber.

Author	Subjects	Intervention	Effect	AEs
O'Keefe ³⁶	13 ICU patients (most with pancreatitis)	32 g/day wheat dextrin up to 5 weeks	Higher fecal SCFA producers and SCFAs.	None reported.
Karakan ⁶⁰	30 ICU patients with pancreatitis	24 g/day mixed soluble and insoluble fiber (open label)	Shorter hospital stays and lower complications.	Self-resolving bloating.
Knight ⁵⁸	259 ICU patients on ventilation	20 g/day mixed fiber synbiotic including 5 g/day inulin	Trend towards lower rates of VAP.	None reported.
Kotzampassi ⁵⁷	65 ICU patients with SIRS	20 g/day mixed fiber synbiotic including 5 g/day inulin	Fewer infections and less diarrhea.	None reported.
Majid ⁶³	22 adults in the ICU	inulin 7g/day	No difference in <i>Bifidobacteria</i> and lower <i>F. prausnitzii</i> .	None reported.
Spapen ⁶⁴	25 ICU patients with septic shock	22 g/L guar fiber enteral feeding, dose individualized	Less diarrhea.	None reported.
Spindler-Vesel ⁵⁹	113 ICU trauma patients	17 g/day average mixed soluble fiber-synbiotic	Fewer infections.	Higher gastric residuals.

6.5 Summary of previous experience with inulin

Our prospective ICU cohort data provides real-world data supporting the hypothesis that inulin, by nourishing SCFA producers, will lead to decreased pathogen colonization and infection in the ICU. Animal studies show that inulin confers protection across various pathogen challenge models and sepsis models including LPS injection and cecal ligation-and-puncture. Ambulatory studies of inulin demonstrate safety and generally show increases in SCFA producers related to inulin. Few ICU studies have tested inulin, but there is ample ICU experience with inulin-like fibers that provides reassurance that high doses of fiber are safe even in the context of sepsis and hypotension in the ICU.

7. Study objectives

The short-term goal of the study is to test inulin for the prevention of MDRO colonization and infection in the intensive care unit. The long-term goal of this research is to develop antibiotic-free strategies that prevent or ameliorate ICU-acquired infections.

8. Study Design

This will be a double-blind, randomized, placebo-controlled trial with two doses.

9. Intervention

Block randomization (blocks of six) will be performed with 1:1:1 random computer allocation of subjects into the three study arms. In the two inulin arms, chicory root-derived inulin (Cargill Inc., Wayzata, MN) will be diluted in 250 ml of sterile water and given at 8 or 16 g twice daily (**Figure 4**). The placebo arm will receive the same volume of sterile water twice daily, with the intervention given for 7 days or until death or hospital discharge. Prior studies suggest that these doses are likely to be safe and sufficient to confer benefit,^{26,36} even in the setting of critical illness.^{57,58,63,65} Subjects, investigators, and the treating ICU team will be blinded to the intervention arm, with blinding managed by the CUMC Research Pharmacy which will provide labeled, de-identified, semi-opaque fluid bags containing inulin/placebo in accordance with the U.S. Code of Federal Regulations governing labelling

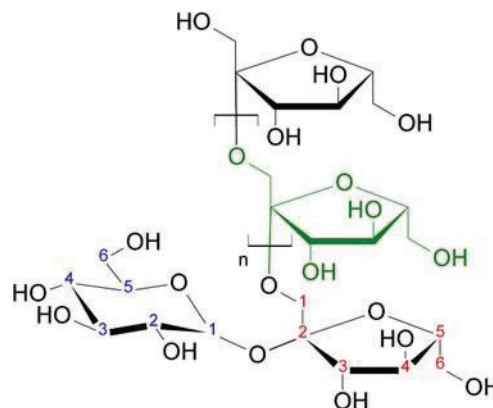


Figure 4. Chemical structure of inulin. Inulin is a naturally occurring polysaccharide derived from chicory root, agave, garlic, and other vegetable sources; it is a long chain carbohydrate of fructose polymers with $\beta(1,2)$ glycosidic linkages which are indigestible by human enzymes but fermented by colonic anaerobic bacteria into short-chain fatty acids (chemical formula: $C_6nH_{10n+2}O_{5n+1}$).

of new investigational drugs (21CFR 312.6). The intervention will be taken orally or given with enteric feeding by nursing staff overseen by the study team, with the first dose administered within 6 hours of ICU admission. The time course for the intervention and remaining study assessments is shown below in **Table 3**.

Table 3. Time course of intervention and main assessments during the study.

Type of Assessment	Inulin ----->			Monitoring ----->			
	Day 0	Day 3	Day 7	Day 14	Day 30	3 months	6 months
Rectal swab	X	X	X	X	X		
Whole stool	X	X	X	X	X		
Clinical data	X	X	X	X	X	X	X
Telephone follow-up						X	X

9.1. Storage, accountability, and dispensing

The study medication will be delivered to the CUMC Research Pharmacy as a powder via Swanson/Cargill protected from moisture and light and accessible only to authorized individuals. The medication will be stored at 20-25°C in powder form and reconstituted before dispensation. Medication labels will be blinded. The Research Pharmacy will maintain a record of the inventory and disposition of all medication and placebo. This receipt record will include from whom the medication was received, to whom it was distributed, the date, quantity, and lot number. The study medication has the following characteristics (**Table 4**).

Table 4: Study medication characteristics.

Product name:	Inulin powder
Manufacturer:	Cargill Inc., 15407 McGinty Rd W, Wayzata MN 55391-2365
Distributor:	Swanson Health, 4075 40 th Ave SW, Fargo, ND 58104-3912
Appearance:	White powder
Flavor:	Neutral to sweet
Bulk density:	0.6 g/mL
Solubility:	>100 g/L
Moisture:	3.41%
Dry stability:	4 years

9.2. Rationale for the selection of duration and dose.

9.2.1. Rationale for duration. Inulin will be given for 7 days with the primary outcomes adjudicated after 3 days. The Day 7 data will be used to test whether an effect can be extended or whether a delayed effect is present. In our cohort data, 84/126 (67%) new infections occurred within 3 days and 97/126 (77%) within 7 days.³⁸ This shows that any ICU-based intervention seeking to prevent infections must work quickly if it is to be effective. Meanwhile, our preliminary cohort data suggests that fiber can have an impact even within this short timeframe (Figure 3). A final assessment will be made on the day of hospital discharge in subjects who are to be discharged prior to Day 14.

9.2.2. Rationale for dose. In the ambulatory setting, inulin impacts SCFA producer levels at doses of 12 to 16 g/day, with biologic effects relevant for ICU patients (e.g., decreases in serum LPS and CRP).^{26,66} Approximately 16 g/day therefore represents the minimum dose at which an effect *might* be seen; this was selected for the low dose arm of the study. However, patients in these ambulatory studies were not critically ill and did not receive antibiotics. It is possible that inulin will have lesser effects in the ICU compared to the ambulatory setting, and logical to test higher doses. To select a maximum study dose, we referenced our own experience with dietary fiber in the prospective cohort and published tolerability data from ICU studies of inulin-like prebiotic fiber. In our prospective ICU cohort, 30 g/day was the maximum observed dose of dietary fiber, and was not associated with any intolerance. In published literature, O’Keefe *et al.* reported tolerance up to a maximum of 36 g/day wheat dextran in the ICU.³⁶ We therefore selected 32 g/day for the high dose study arm because it lies between these values and is exactly double a dose with proven biologic activity.

9.3. Regulatory

No subjects will be enrolled until after review and approval by the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO). The PI holds FDA IND 137359 (FDA date: September 4, 2018) for inulin for the prevention of MDRO colonization/infection in the ICU or other at-risk settings. Safety and adverse effects will be overseen by the PI in conjunction with Daniel Brodie, the Director of Medical Intensive Care Units at our institution, who will serve as the Data Safety Monitoring Officer (DSMO) and will convene an appropriate Data Safety Monitoring Board (DSMB) for the study. Before initiating research, the study will be registered on clinicaltrials.gov.

9.4. Documentation of administration of the intervention

The study team will work with the treating ICU team to ensure that the study drug is delivered in a timely manner. The time and dose of each medication administration will be documented at each study assessment by referring to the documentation of medication administration within the

electronic medical record (EMR). Patients will be enrolled with a goal of administering the intervention within 24 hours of ICU admission and it will be considered a protocol deviation if the intervention is administered more than 48 hours from ICU admission.

10. Outcomes

Primary and secondary outcomes focus on the comparison of baseline to Day 3 samples. This project will also gather samples at ICU Days 7, 14, and 30. These additional samples will be used to construct longitudinal time series data and test for differences between groups that may be slower to emerge (e.g., baseline vs Day 7 comparisons).

10.1. Primary outcome: Relative abundance of SCFA producers through ICU Day 3. The within-individual change in the relative abundance of SCFA producers will be determined by 16S rRNA gene sequencing of rectal swabs and compared between intervention groups. From extracted rectal swab DNA, polymerase chain reaction (PCR) will be performed on a Bio-Rad T100 Thermal Cycler (Bio-Rad, Hercules, CA) to amplify the V4 hypervariable region of the 16S ribosomal RNA gene with primers derived from Klindworth *et al.*⁶⁷ appended with overhang sequences for compatibility with Illumina index and sequencing adapters (Illumina, San Diego, CA). The relative abundance of SCFA producers levels will be determined as the sum total across the bacterial species known to ferment the SCFA butyrate and subtracted within each individual to obtain the change (Day 3 minus baseline).^{39,45,68-70}

10.2. Secondary outcome: MDRO colonization status on ICU Day 3. MDRO colonization status will be based on Day 3 rectal swab cultures, classified categorically and compared between intervention groups. MDROs will be defined as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and MDR Gram negative bacteria⁷¹ (defined as Gram negatives with *in vitro* non-susceptibility for third-generation cephalosporins).⁷² Based on culture results, Day 3 MDRO colonization status will be classified categorically and compared between groups.

10.3. Additional outcomes:

10.3.1. *Feasibility.* Descriptive demographic and clinical data will be compared across study groups to assess adequacy of randomization. Summary statistics (count data) will be recorded for patients across all 3 intervention arms to assess feasibility as (1) the enrollment rate (enrolled)/(enrolled+refusals) over each 12 month period; (2) protocol adherence (proportion of randomized subjects who receive 1 or more doses of the allocated intervention); and (3) fidelity of the intervention (defined as the proportion of high/low inulin allocated vs received and also categorically as receipt of 90% or more allocated doses of inulin across groups). Feasibility goals are as stated in Aim 1.

10.3.2. *Rates of pre-specified AEs.* There will be active ascertainment of AEs in the following categories, which will be compared between intervention groups. This will be done through the end of the intervention period (ICU Day 7) and also through Day 30/discharge to assess for delayed AEs.

- Stool frequency, measured by subject or nursing report by the number of spontaneous stools over the 24 hours preceding each assessment;
- Stool consistency, measured by subject or nursing report as an ordinal variable (0-4) over the 24 hours preceding each assessment;

- Abdominal bloating, measured by subject or nursing report as an ordinal variable (0-3) over the 24 hours preceding each assessment.
- Electrolyte abnormalities, measured by examining for differences in median values, minimum/maximum values, and proportions of values outside the normal range. This will be done for glucose, calcium, magnesium, phosphate, potassium, and sodium.
- Nausea, vomiting, obstruction, and abdominal pain. These will be recorded as present or absent based on bedside assessment of the subject or based on the nursing impression.
- Culture-proven infections, which will be considered both an AE and an outcome (see 10.3.4).

10.3.3. *Antibiotic resistance gene fraction on ICU Day 3.* DNA will be extracted from rectal swabs (MoBio PowerFecal, Carlsbad, CA) and assessed using multiplex quantitative PCR (Qiagen Cat. No. 330261, Valencia, CA) for 87 common antibiotic resistance genes.⁷³ Within-individual differences in multiplex qPCR results will be compared from baseline to Day 3 both as summed changes and within relevant gene categories (e.g., β -lactamase resistance genes) and compared between intervention groups.

10.3.4. *Culture-proven MDR infections through ICU Day 30.* Antibiotic-resistant infections will be defined as those showing all of the following: (1) site-specific symptoms or signs of infection, (2) initiation of targeted antimicrobials by the treating ICU team, and (3) molecular diagnostics or cultures showing an MDRO as adapted from the CDC and NHSN⁷⁴ and previously used by our group (**Table 4**).⁴⁰ Rates of infections will be compared between intervention groups as a sum total, and separately for 3 distinct periods: the intervention period of Day 0 to 7, the Day 7 to 30 period, and the Day 30 to 6 month period.

Table 4. Criteria used to adjudicate culture-proven MDR infections for. Criteria based on CDC/NHSN guidelines.

Criteria	Operationalization	Example
1. Site-specific symptoms or signs of infection.	• Pulmonary: documentation of new or worsening cough <u>or</u> imaging consistent with an infection • Urinary: fever, dysuria, increased urinary frequency, flank pain, mental status changes, or hypotension <u>and</u> clinical exclusion of other causes for infection. • Bloodstream: clinical evidence of a bloodstream infection (fever, chills, or hypotension) without alternative sources for infection • Stool: documentation of new loose stools or frequent stools ≥ 3 per 24 hours • Wound: appropriate surgical site incision or wound with discharge, warmth, or erythema.	Cough and a chest X-ray showing new infiltrate.
2. Positive cultures or other diagnostics with an MDRO.	• Pulmonary: quantitative or semi-quantitative sputum or bronchoscopic cultures • Urinary: $\geq 10^5$ CFU/mL growth. • Bloodstream: growth of a recognized bloodstream pathogen from blood but not another site <u>or</u> growth of a NHSN commensal from blood but not another site.	Sputum culture growing $>10^5$ CFU/ml of <i>K. pneumoniae</i> resistant to ceftriaxone.

- Stool: positive PCR for the *C. difficile* toxin B gene (Cepheid or BioFire) or positive toxin B EIA
- Wound: growth of aseptically obtained organisms.

3. Initiation of targeted antibiotics within 24 hours.	Antibiotics showing non-susceptibility using standard CLSI breakpoints or appropriate empiric antibiotics initiated at the time of clinical suspicion/testing and continued for ≥ 3 days <u>or</u> initiated within 24 hours following the availability of diagnostic testing showing a culture-proven infection.	Initiation of ceftriaxone when the X-ray was ordered; later changed to meropenem.
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10.3.5. *Fecal SCFA levels.* The SCFAs butyrate, acetate, and propionate will be measured from whole stools on a 6490 triple quadrupole mass spectrometer and compared between intervention groups using the first stool sample produced after the Day 3 assessment. Patients who fail to produce a stool from Day 3 to 7 will be excluded from this analysis.

10.3.6. *Proportion of goal calories through ICU Days 3 and 7.* Proportion of goal calories consumed will be defined by manually extracting data from electronic nursing flow sheets. Intake during the intervention be calculated by multiplying enteral or oral feeding caloric content by the flow rate or percentage of meal consumption. A patient-specific calorie target will be calculated by a registered clinical dietician using the Mifflin-St. Jeor equation and the Penn State 2003b and 2010 equations, taking into consideration age, body mass index, ventilation status, and comorbidities.⁷⁵ The proportion of goal calories consumed will then be calculated as observed nutritional intake divided by calorie target. Day 3 and Day 7 proportions will be compared between intervention groups.

10.3.7. *Length of ICU stay.* Length of ICU stay through Day 30 will be compared between treatment groups, with Fine and Grey methods used to adjust for death as a competing risk. Length of ICU stay will be measured from the first to the last set of recorded ICU vital signs.

10.3.8. *Length of hospital stay.* Similarly, length of hospital stay through Day 30 will be compared between treatment groups, again adjusting for death as a competing risk. Length of hospital stay will be measured from the first set of recorded ICU vital signs to the last set of hospital recorded vital signs.

10.3.9. *Mortality through ICU Day 90.* Death data will be extracted from the hospital EMR which immediately captures in-hospital death and receives monthly mortality updates from the National social security death index. Kaplan-Meier methods will be used to compared 30- and 90-day mortality between treatment groups.

10.3.10. *Self-assessed quality of life at 6 months.* Subjects or their caregivers will complete the EQ-5D-5L⁷⁶⁻⁷⁸ and Katz ADL questionnaires^{79,80} to test their quality of life at 3- and 6 months post ICU admission. Composite data will be compared between intervention groups.

10.3.11. *Time series data including Day 7 outcomes.* Time series data will be built and visualized for all relevant outcomes. We will explore the possibility of a delayed effect by testing for differences between groups from baseline to Day 7. If there is an observed effect, the Day 14 and Day 30 data will allow us to assess its durability.

11. Study population

11.1. Study setting

Patients will be enrolled from medical ICUs affiliated with Columbia University Medical Center. These ICUs include but are not limited to the following locations, all of which are in the general vicinity of Columbia University's medical campus:

ICU short designation	Full name	Hospital building, floor location	Street address
MICU-A	Medical ICU-A	Milstein, 4 th floor	177 Fort Washington Ave, NY, NY
MICU-B	Medical ICU-B	Milstein, 4 th floor	177 Fort Washington Ave, NY, NY
NICU	Neurological ICU	Milstein, 8 th floor	177 Fort Washington Ave, NY, NY
AICU	Allen ICU	Allen Pavilion, 2 nd floor	41 Broadway, NY, NY

The study will enroll 90 consecutive adult ICU patients who meet criteria for sepsis, are receiving appropriate antibiotics, and can complete a bedside assessment within 4 hours of ICU admission and receive the trial intervention within 6 hours of ICU admission. A replacement strategy will be used. If subjects are randomized but fail to receive the intervention or complete the Day 3 assessment, an additional subject will be enrolled to take their place with a final target enrollment of 30:30:30 patients who complete a minimum of 3 days of assessments. Specific inclusion and exclusion criteria are as follows:

11.2. Inclusion criteria

- Medical ICU. Subjects will be newly admitted to one of two CUMC medical ICUs during the study enrollment period;
- Age. Subjects will be eighteen or more years old at the time of ICU admission;
- Sepsis. Subjects will meet criteria for sepsis with life-threatening organ dysfunction caused by infection (Sepsis-3 third international consensus definition, 2016).⁸¹ According to this definition, life-threatening organ dysfunction is operationalized as an increase in the Sequential [Sepsis-Related] Organ Failure Assessment (SOFA)⁸² score of ≥ 2 points above baseline. Sepsis-3 criteria also require patients to have a known or suspected infection, defined as sampling of blood or any other body fluid for infection with concurrent administration of appropriate antibiotics (see Table 4);⁸¹
- Appropriate antibiotics. Subjects will receive appropriate antibiotics, which will be operationalized as (1) among subjects with positive culture data, the antibiotics within classes where the organism is susceptible based on standard Clinical and Laboratory Standards Institute (CLSI) cut-offs⁷²; or (2) among subjects receiving empiric antibiotics (i.e., with negative cultures), antibiotics within classes with significant anaerobic activity. This will include β -lactam/ β -lactamase inhibitor combination antibiotics, cephalosporins (generation 2 or greater), fluoroquinolones, lincosamides (clindamycin), metronidazole, and monobactams (a.g., meropenem). Vancomycin monotherapy is intentionally excluded. Antibiotics must be received within 24 hours before ICU admission or be actively ordered at the time of bedside screening;

- Prompt intervention. Subjects will complete study enrollment within 4 hours of ICU admission so that the intervention can be administered within 6 hours of ICU admission. The first set of recorded ICU vital signs will define the time of ICU admission.

11.3. Exclusion criteria

- Inability to receive oral or enteric fluids. Patients will be excluded if they are *nil per os* or are unable to take fluid by mouth or delivered via enteric nasal or oral tube because they would be unable to receive the study intervention;
- Inulin allergy. Patients will be excluded for safety reasons if they have a known chicory allergy. Serious chicory allergies are exceedingly rare although mild respiratory symptoms and IgE-mediated food allergies have been reported;⁸³
- Hyponatremia. Patients will be excluded for hyponatremia with serum sodium ≤ 128 mEq/L because the intervention will be delivered in 500 ml of free water daily. If subjects develop hyponatremia (serum sodium serum sodium 125-128 mEq/L) after enrollment and randomization which persists at the time the subject is due to receive the study intervention, the study team will confer with the treating ICU team regarding whether the intervention should be deferred or further concentrated in order to minimize free water. If subjects develop severe hyponatremia (serum sodium serum sodium ≤ 124 mEq/L) after enrollment and randomization, the intervention will be withheld until 2 consecutive serum sodium values are within normal limits;
- Immunosuppression. Patients will be excluded if they have immunosuppression, as CD4 count < 200 or absolute neutrophil count < 500 or reasonable expectation of either during the study intervention period. We believe that the inulin works by modifying the gut bacteria. Excluding patients who lack the ability to mount an immune response improves trial homogeneity;
- Surgery involving the intestinal lumen. Patients will be excluded for surgeries involving the intestinal lumen within 30 days. The most common side effects from inulin are subjective bloating and abdominal distension.^{26,28,30,52} Although this bloating appears to be mild and self-limited, patients with recent bowel surgeries may be at greatest risk for such symptoms and will therefore be excluded;
- DNR or DNI status. Such patients have limited treatment goals and will be excluded to minimize heterogeneity;
- No LAR. Patients will be excluded if they lack capacity for consent and have no appropriate Legally Authorized Representative (LAR) to act as surrogate decision-maker.

12. Enrollment strategy

Patients will be identified at the time of ICU bed allocation and screened for inclusion/exclusion criteria. After consultation with the treating ICU team, subjects who meet screening criteria will have the eligibility evaluation completed at the ICU bedside. This will be done after first obtaining agreement from the medical ICU attending of record that the patient/surrogate can be approached for the study. We anticipate that $> 50\%$ of patients will lack decision-making capacity and will accept consent from a surrogate in these situations, as previously described by our group.³⁷ Issues related to altered capacity, privacy and time for decision-making, consent of LARs, and ongoing consent are discussed in detail in the **Human Subjects and Recruitment and Safety**

Procedures section. We expect that patients will usually be initially enrolled with surrogate consent. Patients who are on study will then be reassessed for capacity at each interaction, with the final determination of capacity made by the treating ICU team. When subjects regain capacity, they will make their own determination of whether or not to continue in the study. If subjects do not regain capacity by the time of hospital discharge, surrogate consent will be accepted as final. This approach, which we have used before,³⁷⁻³⁹ preserves complete patient autonomy while recognizing that the target population for the study is unlikely to have decision-making capacity at the time of ICU admission.

Compliance statement regarding consent

This research will meet the requirements of **10 U.S. Code 980** for experimental human subjects research that “(1) the informed consent of the subject is obtained in advance; or (2) in the case of research intended to be beneficial to the subject, the informed consent may be obtained from a legal representative of the subject.”

Retention

Potential loss of patients after randomization will be from death/discharge prior to ICU Day 3, or withdrawal of consent (e.g., after initial surrogate consent). In our ongoing ICU cohort studies, there has been 11.3% mortality within 3 days and a 0% Day 3 discharge rate. Additional patients will be enrolled for patients who do not complete the Day 3 assessment due to death or discharge. Thus, we expect to enroll 102 patients to obtain 90 who are able to donate a Day 3 sample and therefore can included in the intent-to-treat analysis.

12.1. Randomization and blinding

Randomization and data entry will take place through a secure, web-based system managed by the CUMC Data Coordinating Center (DCC) headed by Howard Andrews. This password-protected system is based on the Research Electronic Data Capture (REDCap) platform. The Research Nurse will use paper clinical research forms (CRFs) to document the initial screening process. When this information is entered into REDCap, the system will automatically generate a subject identifier and randomization code using 1:1:1 randomization in randomly permuted blocks of 6. This randomization code will be electronically communicated to the research pharmacy along with a separate key which will allow them to identify the random assignment. The Columbia Research Pharmacy will prepare the study intervention in indistinguishable semi- opaque fluid bags. Although inulin is readily soluble at the study doses, the opacity of these bags will eliminate any possibility that a small amount of precipitant might reveal the study assignment to the ICU nurses who deliver the intervention. Five drops of non-caloric flavoring syrup (McKesson Supply, Yonkers, NY, Product #570727) will be placed into the reconstituted inulin/placebo to prevent any possibility of accidental unblinding based on taste in patients who are alert. The patient, treating ICU team including the ICU nurse, and study team will remain blinded to each assignment until the completion of the trial, with the DCC preparing unblinded safety reports for the DSMO at pre-specified intervals.

12.1.1. Clinical need for unblinding

It seems unlikely that clinical need for unblinding will arise. If this occurs, the PI will coordinate with the DCC to facilitate unblinding for the treating ICU team. In any case of unblinding, data collection and follow-up will be maintained and the patient analyzed per-protocol.

12.2. Delivery of the intervention

The treating medical team will order the study intervention as a non-formulary medication to be delivered by ICU nurses, as they would any other medication, and the study team will work to ensure prompt delivery of the intervention with a goal of having it delivered within 24 hours from

the first set of ICU vital signs.

Delivery of the intervention will be managed by ICU nurses who are not part of the study team by encouraging the subject to drink the liquid formulation or, in subjects who are not taking oral medications, by attaching the intervention to the patient's oral or nasogastric tube. The time of dosing will be recorded electronically within the patient EMR and documented by study staff on the CRFs and within REDCap.

12.3. Premature cessation of the intervention

Efforts will be made to ensure that all subjects who are randomized receive the study intervention. The initial medication order will specify that the study intervention is to be given q12h for a total of 14 doses. The study intervention will be stopped under the following conditions:

- Death;
- Discharge from the hospital;
- Request to withdraw from the study by the patient or surrogate. This request can be made at any time, without providing a reason. Consent to continue data collection and retain samples already collected will be sought in these situations;
- Definite clinical indication or contraindication becomes apparent. If the treating ICU team feels at any time that the patient needs or should not have fiber supplementation, the intervention will be immediately halted. The patients will remain in the study for follow-up and the intervention will be held as long as the indication/contraindication remains. In general, if the indication/contraindication resolves within the 7 day timeframe of the intervention, the intervention will be resumed. If the intervention is withheld for hyponatremia, the intervention will be resumed only once 2 consecutive serum sodium values are within normal limits;
- Adverse or serious adverse event related to the study intervention. Such events will constitute unanticipated problems. The patient will remain in the study for follow-up, but no further interventions will be administered.

13. Study assessments

The total study duration will be no more than 30 days of bedside assessments and no more than 6 months of telephone follow-up, both measured from the first recorded set of ICU vital signs. Samples will be gathered and bedside assessments made at the following intervals after ICU admission or until hospital discharge/death: baseline, 3 days, 7 days, 14 days, and 30 days. During study assessments, data will be combined from the following sources: (1) samples collected by the study team, (2) bedside assessments, and (3) data from the EMR.

13.1 Sample collection and storage

Sample collection is focused around **rectal swabs** because the timing of swabs (as opposed to whole stools) can be precisely dictated and because rectal colonization with MDR bacteria best reflects overall MDR colonization status⁸⁴⁻⁸⁸ and risk for subsequent infection.⁸⁹ Samples are described below.

- Rectal swabs. At each study assessment, deep flocked nylon swabs of the rectum will be performed in duplicate to allow independent processing of swabs for 16S rRNA gene sequencing/multiplex qPCR and for bacterial culture of MDROs. Swabs will be inserted 5 cm rectally with patients in the left lateral decubitus position and rotated 5 times, with adequate

sampling verified by looking for fecal staining. Swabs to be sequenced will be flash-frozen at -80°C for long-term cold storage⁹⁰ and batched extraction;⁹¹ swabs to be cultured will be transported on soy broth with 20% glycerol (Becton Dickinson, Franklin Lakes, NJ) for culture or, when culture cannot be performed immediately, for storage overnight at 4° C and culture the following morning.⁹²

- Whole stools. Nursing staff will collect the first spontaneous whole stool subsequent to each study assessment. 4 x 8 ml aliquots of stool will be flash-frozen and stored at -80 ° C.
- Oral swabs. Two cotton-tipped oral swabs will be used to gather a composite of the oral flora by brushing the following consecutive locations x 10 each: left cheek, right cheek, hard palate, tongue, floor of the mouth, and maxillary gingivae (same as the Human Microbiome Project).⁹³ Swabs will be flash frozen at -80 ° C.
- Urine. ICU nurses will withdraw 2 x 8 ml of urine using standard technique from the urinary catheter sampling port. In patients who lack a urinary catheter, clean catch urine samples will be accepted and aliquoted as above.
- Blood. Residual blood from clinical samples drawn immediately prior to each study assessment will be retrieved by the study team. For each subject, one 6 mL serum-separator and one 8 mL EDTA tube will be retrieved. Buffy coat will be separated by centrifuge and with 1-2 mL aliquots generated for plasma/buffy coat and stored at -80 ° C. This strategy spares subjects the need for an additional blood draw.

Oral swabs, urine, and blood will be stored for future testing. The rationale for collecting these additional samples is that they are non-invasive, can be easily collected, and will provide opportunities for future studies seeking to explore additional markers or mechanisms (e.g., urinary 3-indoxyl sulfate for gut microbiome disruption⁹⁴ or micro-RNAs in sepsis).⁹⁵ All sample storage will be in the PI's -80°C freezer unit (P&S-8) except for the fresh rectal swab used for culture which will be stored within the Uhlemann lab (P&S-9). Assays performed from rectal swabs and whole stools (SCFAs) are described below.

13.2. Sample assays

The assays described below will be performed from rectal swabs or whole stools (for fecal SCFA levels). Residual sample material will be retained in -80°C storage for the duration of the study.

- 16S rRNA gene sequencing. 16S rRNA gene sequencing will be performed to determine the **primary outcome**. From extracted rectal swab DNA, polymerase chain reaction (PCR) will be performed on a Bio-Rad T100 Thermal Cycler (Bio-Rad, Hercules, CA) to amplify the V4 hypervariable region of the 16S ribosomal RNA gene with primers derived from Klindworth *et al.*⁶⁷ appended with overhang sequences for compatibility with Illumina index and sequencing adapters (Illumina, San Diego, CA). Samples will be purified with Agencourt AMPure XP beads (Beckman Coulter, Jersey City, NY) and quantified using the Quant-iT broad range dsDNA Assay Kit (Thermo Fisher Scientific, Fair Lawn, NJ). Libraries will be normalized, pooled, and denatured in preparation for cluster generation and sequencing, which will be performed on the Illumina MiSeq 300PE.
- Bacterial culture. Aerobic culture will be performed to determine the **secondary outcome**. Culture has been selected for the primary outcome because culture identifies viable bacteria, remains the most common clinical method for testing for MDRO colonization in

the ICU, and best predicts longterm risk for organism-specific infection.⁹⁶⁻⁹⁹ Additional analyses will utilize alternative methods for classifying MDROs. Cultures will identify MRSA, VRE, and MDR Gram negatives, which cause 94% of all MDR bacterial infections in the ICU.⁶ Rectal swabs will be gently vortexed to dissociate DNA from the swabs into the broth media. Media will then be split into equal aliquots and plated under a laminar flow hood for MRSA (Spectra-MRSA, Remel), VRE (Spectra-VRE, Remel), and ESBL or *Klebsiella pneumoniae* carbapenemase (KPC)-producing bacteria (Uhlemann lab). In addition, we will plate cultures on Gram-negative selective agar (MacConkey II agar, Becton Dickinson) directly and at three serial dilutions for semi-quantitation (10^{-2} , 10^{-4} , and 10^{-6}). While the main analysis will be based on a categorical classification of MDROs (present vs absent), an exploratory analysis will be conducted using semi-quantitative culture data. Preliminary data show that these dilutions will yield a countable number of colonies. After 18-24 hours of aerobic growth, selective plates will be classified as positive vs negative for growth according to the media characteristics. The colony-forming units (CFUs) on the non-selective plates for Gram positives/negatives will be counted to provide relative quantification of each MDRO based on the total CFU counts from the non-selective plates. If multiple non-selective plates show growth, the plate with 10-100 colonies will be used for CFU counting with results normalized to the 10^{-2} plate. From these plates, organisms will be identified using the VITEK 2 system (bioMerieux) and AST-N010/020 cards with confirmatory testing as needed. Resistant isolates will be stored for whole genome sequencing analyses.

- **Quantitative PCR.** Quantitative PCR for resistance genes will be performed as an additional outcome. DNA will be extracted from rectal swabs (MoBio PowerFecal, Carlsbad, CA) and assessed using multiplex quantitative PCR (Qiagen Cat. No. 330261, Valencia, CA) for 87 common antibiotic resistance genes.⁷³ In this assay, 250 ng of template genomic DNA will be added to each reaction on a 96-well plate which will be run on a StepOnePlus RT-PCR machine using the following cycling conditions: initial denaturation for 10 min at 95° C, cycling 45 x 15 sec at 95° C denaturing followed by 2 min at 60° C annealing and extension. Controls will detect the presence of bacterial DNA, PCR inhibitors and background (no template control (NTC)). PCR cycle thresholds (C_T) of <35 will be considered positive for the presence of any given gene. Adequate reactions will be determined by C_T values of <29 for pan-bacterial reference genes (e.g., *16S rRNA*, *gyrA*, *recA*, *rpoB*)¹⁰⁰ and positive PCR controls (PPC) C_T values of <24. Linearity and sensitivity for this PCR have been determined using synthetic templates over a 6-log serial dilution ranging from 1 to 1 million copies, with results verified across multiple antibiotic resistance genes using pyrosequencing.⁷³
- **Fecal SCFA levels.** Fecal SCFAs levels will be assayed as an additional outcome. Whole stools will be aliquoted and diluted with 80% ethanol to be agitated at 4°C. After centrifugation, 20 µl of supernatant from the homogenized samples will be mixed with 20 µl of 200 mM N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1-EDC HCl) in 5% pyridine and 40 µl of 100 mM 2-Nitrophenylhydrazine (2-NPH) in 80% acetonitrile (ACN) with 50 mM HCl. After a brief incubation, ACN will be added to the solution which will be injected onto a 6490 triple quadrupole mass spectrometer (Agilent, Santa Clara, CA) and tested for concentrations of the SCFAs butyrate, acetate, and propionate.

13.3. Bedside assessments including data gathered from the EMR

During each study assessment, a study-specific Case Report Form (CRF) will be used to record the following data: origin for admission (classified as from the hospital floor, operating room, emergency room, or outside ICU transfer based on the most recent location prior to CUMC ICU

admission); the Glasgow Coma Scale (GCS);¹⁰¹ the use of life support (classified as present vs absent) including the use of mechanical ventilation, hemodialysis, or additional life-support devices such as extra-corporeal membrane oxygen (ECMO) or an intra-atrial balloon pump (IABP); and the presence or absence of intravenous lines or catheters including a central venous catheter, urinary catheter, arterial catheter, nasal or oral gastric tube, or rectal tube. Using duplicate data entry, anonymized CRF data will be transferred into the secure REDCap database. Additional clinical variables will be entered directly into REDCap from the EMR. These variables will include laboratory analyses, all of the component variables of the Sequential Organ Failure Assessment (SOFA) score,⁸² measures related to nutritional intake, and ICU interventions including administration of vasopressors, proton pump inhibitors, and antibiotics (with the name of the antibiotic and route of administration recorded).

13.3.1. Tolerability

Patients who are alert will be asked regarding abdominal bloating which will be graded on a 4-point Likert scale (0=none, 1=a little, 2=a moderate amount, 3=a lot/severe). When patients are not alert, this will be graded as “unable.” ICU nurses will be asked to grade the average consistency of stools within each preceding 24 hours on a 5-point scale (0=like water, 1=like porridge, 2=loose but with chunks, 3=formed, soft, 4=formed, hard). This information will also be recorded from the EMR into REDCap as a separate entry. When subjects have no stools within the preceding 24 hours, this will be recorded as “no stools.” The frequency of stools within the preceding 24 hours will be recorded as an integer at each study assessment. Again, this will be done based both on the nurse’s in-person report and separately based on EMR documentation.

ICU nurses will be additionally asked regarding the presence or absence of the following symptoms during the 24 hour period prior to each study assessment: nausea, vomiting, bowel obstruction, and abdominal pain. This data will be recorded categorically on the CRFs/REDCap and will appear on DSMO reports.

13.3.2. Nutritional intake

Information related to nutritional intake will be gathered from the EMR including goal calories, actual calories consumed, and the amount of dietary fiber consumed in grams. All ICU patients at our institution receive a complete clinical nutritional assessment with calculation of goal calories based on the Penn State Equation¹⁰² with the modified equation used for individuals >60 years old or those with BMI >30 as described by Frankenfeld *et al.* in 2009.^{103,104} Actual calories and grams of fiber consumed will be based on the specific components of the tube feeds received or, among patients on an *ad lib* diet, the food consumed. The nutritional components of all CUMC diets are completely specified in terms of calories, fat, protein, carbohydrate, and fiber content. To calculate calories and fiber consumed, the study team will refer to the proportion of each meal consumed as recorded by ICU nurses and to the volume of tube feeds delivered which is captured hourly in the EMR. In those receiving tube feedings, the interval number of tube feeding interruptions will be recorded at each assessment or recorded as 0 in those receiving *ad lib* diets.

13.3.3. Long-term telephone follow-up

Telephone interviews will be conducted with subjects or their surrogates 3 months after ICU admission and again 6 months after ICU admission. In the event that subjects are still hospitalized, these interviews will be conducted at the bedside. Vital status will be ascertained and, to minimize loss of follow-up information, we will interview subjects or surrogates to determine (1) discharge location type (classified as home, short-term rehabilitation, or long-term rehabilitation including skilled care facilities), (2) hospital admission to non-CUMC facilities after ICU discharge, (3) physician office visits after ICU discharge, and (4) infections or other adverse events after ICU discharge. If there are non-CUMC hospital admissions or other healthcare

interactions, permission will be requested to obtain relevant records to determine the nature of infections and to assess for potential medium- to long-term AEs related to the study intervention. Among surviving subjects, the EQ-5D-5L (EuroQol 2009) will be used to determine health status across the domains of mobility, self-care, activity levels, pain, and anxiety/depression.^{76,77} Use of this highly validated instrument will facilitate standardization and generalizability of results and will provide preliminary data for post-ICU discharge monitoring for later phase trials. This instrument can be applied via telephone in 5 minutes and was recommended in 2017 for post-ICU assessment of overall well-being after a three-round modified Delphi process involving clinical researchers from over 16 countries, patients/caregivers, clinicians, and research funders.⁷⁸ EQ-5D-5L responses have the potential to vary depending on whether answers are provided on patients versus surrogates,¹⁰⁵ and therefore we will additionally assess post-ICU disability using Katz' Index of Independence in ADLs (Activities of Daily Living).⁷⁹ Although focused on functional status rather than well-being, Katz' ADLs has been validated as an important patient-centered outcome across dozens of populations and unlike the EQ-5D-5L has high agreement between patients and caregivers.⁸⁰

14. Data collection and management

The Columbia DCC will oversee use of a custom-designed, REDCap-based clinical trial data management system. REDCap is a widely used web-based relational data system developed at Vanderbilt University with NIH support to collect research information in 21CRFPart11, FISMA and HIPAA-compliant environments. REDCap functionality that will be used in this trial include randomization, subject scheduling, *ad hoc* reporting, data verification and audit trails. Paper CRFs will be used to collect bedside data, while readily available selected electronic data (e.g., laboratory values) will either be directly “pulled” from Columbia clinical servers and merged into the REDCap database or manually entered into REDCap. REDCap ‘Events’ will be specified corresponding to the study assessment timepoints: baseline, Days 3, 7, 14, 30, 3 months, and 6 months. Data of each type will be associated in the system with the appropriate time period. REDCap “Anytime” functionality will be used to capture adverse events and other incidents that can occur at any time, i.e. events that are not associated with fixed time periods. The REDCap system has built-in data verification aspects that will be utilized for the trial including minimum and maximum ranges and other logical checks, and automatic checks for completion of individual items and forms.

14.1. Data security within REDCap

The servers on which DCC REDCap project data are stored are located in a physically and electronically secure environment maintained by institutional IT staff on the CUMC campus. The DCC confirms project data access privileges on a monthly basis, and REDCap requires strong passwords, which must be changed periodically. In this trial, to ensure data security, explicit identifiers needed for recruitment and scheduling (names, addresses, phone numbers, email addresses, medical record numbers) will be maintained separately and will *not* be stored in the REDCap database.

14.2. Record retention

All electronic and paper records will be retained for a minimum of 6 years from the trial end date in accordance with New York State law and meeting or exceeding Federal minimums. Consent forms, CRFs, and other relevant paper documents will be moved to secure longterm paper storage once the trial has been closed and the data locked. Record retention will be prolonged beyond 6 years as necessary if required by the funding agency.

15. Safety and adverse events (AEs)

Adverse health events, laboratory irregularities, and even death are expected in ICU patients with sepsis and it would be difficult or impossible to accurately document and label all adverse health events. This is a common problem faced by ICU trials. The solution recommended by academic critical care research groups (e.g., Cook *et al.*) is to pre-specify AEs of interest for careful monitoring. In keeping with this approach, this study will produce detailed reports of these AEs for the DSMC at standard intervals while only unanticipated problems that also meet criteria for serious adverse events (SAEs) will be reported to the DSMC in real time.¹⁰⁶ AEs will be reported for all individuals who have received one or more doses of the intervention. This study has pre-specified AEs in the following categories.

- Bloating: graded 0-3 based on patient report: patient mean and maximum values will be reported;
- Stool consistency and frequency: graded 0-4 for consistency and with an integer denoting frequency over 24 hours based on nursing report. For each patient, mean and maximum values will be reported;
- Electrolyte imbalances: For each patient, the minimum and maximum values for serum calcium, magnesium, phosphate, potassium, and sodium will be reported. This will be done for the 7 days of the intervention period and separately from Day 7 through Day 30/discharge;
- Gastrointestinal AEs: the gastrointestinal AEs of nausea, vomiting, bowel obstruction, and abdominal pain will be recorded as present or absent for each assessment and separated from other AEs to improve early pattern recognition by the DSMO;
- Infections: Infections are both an AE and an outcome and will be adjudicated as previously described. For each infection, the date of the infection, suspected site, organism, and antibiotics received will be recorded. Infections will be further classified as MDR vs non-MDR using the criteria previously described;
- Death: death will be gathered from the hospital EMR, which interfaces with the social security death index.

15.1. Serious adverse events

Federal Regulation 62 Oct. 7, 1997 defines SAEs as those events occurring at any dose which:

- Result in death;
- Are life-threatening, meaning the patient was at risk for death at the time of the event;
- Require hospitalization or prolong hospitalization;
- Results in significant disability or incapacity;
- Is a congenital abnormality/birth defect;
- Or does not meet these criteria but is thought by the investigator to be unusual and potentially serious.

SAEs in this trial will be AEs meeting the above Fed. Reg. 62 definition.

15.2. Adjudicating and reporting adverse events as unanticipated problems

Unanticipated problems (UPs) will be any unforeseen medical event thought likely related to the study intervention. Such events will be monitored for in real time. UPs that do not meet criteria for seriousness (same as SAE criteria) will be reported to the DSMO and IRB at pre-specified intervals. UPs that meet criteria for seriousness will be reported within 24 hours from our notification of the event. This reporting will include:

- Contact of the DSMO;
- Contact of the Columbia IRB;
- Fax or email scan containing when the event occurred, the name of the reporter, callback information, the protocol number, and a description of the event;
- Availability of the PI to provide follow-up information regarding the event.

The proposed research is pending review by the Columbia University IRB (IRB #AAAS2576) and will be reviewed by the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO) prior to implementation. Prior to initiation of research, the study will be registered on clinicaltrials.gov.

Safety and adverse effects will be overseen by the PI in conjunction with the Data and Safety Monitoring Officer (DSMO). **Daniel Brodie**, the Director of the Medical Intensive Care Units at our institution will serve as the trial DSMO and will convene an appropriate Data and Safety Monitoring Committee (DSMC) to oversee interim study results. The primary responsibility of the DSMC will be to review interim data in terms of safety and make recommendations whether the study should be changed, halted, or terminated. Full details of the DSMC procedures and processes as well as additional details regarding AE and SAE reporting are in the DSMP.

15.2.1. Compliance statement regarding research monitoring

The DSMB under Dr. Brodie will function as a **Research Monitor** and is responsible to oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

15.3. Unblinding for adverse events

All possible efforts will be made to retain blinding for the duration of the trial. However, if a treating clinician feels that blinding must be removed in order to assess a possible adverse reaction quickly and correctly, the PI will facilitate this process by working through the DCC.

16. Study termination and completion

The study may be terminated at any time for safety concerns by the PI, DSMC, IRB, or other appropriate regulatory bodies. Otherwise the study will continue until 90 patients are enrolled who complete the Day 3 assessment and will be considered complete when all study assessments and analyses have been concluded.

17. Statistical methods

17.1. Overall plan for statistical analysis

After enrollment is complete, the REDCap dataset will undergo DCC cross-checks for quality and accuracy. The PI will review blinded data to identify errors which, if they exist, will be rectified by reference to paper CRFs or to the EMR. After quality checks are complete, the REDCap dataset will be closed and locked. The biostatistician will then perform an intent-to-treat analysis to determine the primary and secondary outcomes. The DSMO will have complete access both to the raw data and to the analytic code used by the biostatistician and will nominate a qualified monitor who will review this work for rigor. Once this is complete, the primary and secondary outcomes will be finalized. At this point, the locked data will be made available to the PI and other investigators for additional analyses. For all analyses, $\alpha < 0.05$ will be considered statistically significant and two-sided testing will be performed. When death is a competing risk, Fine and Gray regression analyses will be performed.

17.2. Determination of the primary and secondary outcomes

Primary outcome: within-individual change in relative abundance of SCFA producers. 16S rRNA gene sequencing data will be processed using the QIIME platform with appropriate rarification and filtering.¹⁰⁷ The primary analysis will be intent-to-treat, restricted to the subjects who complete the Day 3 assessment and contribute data. Within-individual change in SCFA producers will be calculated as Day 3 minus baseline relative abundance and an ANOVA or Kruskal-Wallis (KW) test (if skewed data) will be used to assess for differences across the three groups. If there is no significant difference between the low- and high-dose inulin arms, these arms will be combined for comparison against placebo in the final analysis using a two-sample t-test or rank-sum test. Although the primary analysis will be with the Day 3 samples, unadjusted and adjusted longitudinal data analysis will be performed using the generalized estimating equation approach with working independence correlation structure.

Secondary outcome: MDRO colonization. Subjects who culture positive from rectal swabs from Day 3 for MRSA, VRE, or a Gram negative with non-susceptibility to a third generation cephalosporin will be classified as MDRO colonized and all other subjects as not MDRO colonized. The proportion of patients who are MDRO colonized on Day 3 will be compared between intervention groups using a chi-squared test or Fisher's test. For this analysis, patients in the inulin arms will be combined if testing shows no significant difference between these inulin arms. Because baseline colonization status is likely to be an important predictor of Day 3 colonization status, we will test whether baseline MDRO colonization rates differ between intervention groups. If such a difference is observed, we will reanalyze Day 3 MDRO colonization with stratification according to baseline MDRO colonization (baseline MDRO colonized vs not colonized). Exploratory analyses will examine Day 7 MDRO colonization status and semi-quantitative culture data using ANOVA or Kruskal-Wallis testing. The difference in rates of Day 3 MDRO colonization will be taken as the effect size estimate for future trials.

17.3. Power calculation and sample size

Primary outcome: within-individual change in relative abundance of SCFA producers. The study is powered to detect a difference in SCFA producer levels that is equal to or greater than the observed difference in SCFA producer levels from our prospective cohort (6.6% for high vs 3.7% low dietary fiber). The rationale for this is that inulin must be at least as impactful as mixed dietary fiber to be a viable therapeutic. The proposed sample size of 30:30:30 will yield 80% power to detect a minimum difference of 0.73 standard deviations (SD) comparing any one inulin arm to the placebo arm using a two-sided t-test with 0.05 significance level and assuming equal variance. If the inulin arms have similar changes in SCFA producer levels, they will be combined and the study would have 80% power to detect a minimum 0.63 SD for inulin compared to placebo at the .05 significance level. This sample size will also have 80% power to detect 0.33 SD differences among the 3 means versus the alternative of equal means using an F-test at the .05 significance level.

Secondary outcome: MDRO colonization. Power calculations were performed using the observed 42% rate of MDRO colonization in our prospective ICU cohort and 1:1:1 allocation to the intervention. Because this is an early phase study conducted with the expectation that promising results will be followed up by definitive larger studies, sample size calculations are based on one-sided testing with alpha .10 using a t-test based on the binomial distribution. Under these assumptions, a sample size of 90 patients will yield 80% power to detect a 20.4% or less rate of MDRO colonization on Day 7 with inulin, assuming that the two inulin arms are combined. If the inulin arms are not combined, there will be 80% power for a 17.3% or less rate of Day 7 MDRO colonization comparing any one inulin intervention arm vs placebo. The two-sided 95% confidence interval for the effect size estimate within the combined inulin arms would be 7.1 to 26.6% for an estimate centered on 15% and 10.8 to 32.3% for an estimate centered on 20%.

17.4. Interim analyses

Interim analyses will be performed for safety, and the DSMC will have the ability to halt the trial at any time. Full DSMP reports will be produced after 10, 20, 30, and 45 patients are randomized and at least semi-annually based on the date of enrollment of the first patient. Toxicity monitoring will be performed using a frequentist approach and targeting an excess rate of toxic death of no more than 5%. Toxicity will be monitored for each arm at the same 4 time points. Sequential boundaries will be calculated using the Pocock method. If the number of toxicities differs in any one study by 3, 4, 5, or 7 patients corresponding to the assessments above, enrollment will be halted and toxicities will be further evaluated to assess if it is appropriate to terminate the study. This stopping boundary yields a probability of early stopping of at most 0.05 when the dose-limiting toxicity is equal to 0.05. Toxic death will be adjudicated by the DSMC. There are no plans for futility monitoring because of the relatively small size of the proposed trial, non-invasiveness of the samples collected, and the potential for longitudinal study results to add significant mechanistic understanding to MDRO colonization in the ICU.

18. Publication policy

Study results will be disseminated as widely as possible by publication and presentation. The PI is ultimately responsible for publications arising from the study. Funding sources will be recognized.

Appendix A: References

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Appendix B: Abbreviations and terms

ADLs	activities of daily living
AE	adverse event
ANOVA	analysis of variance
APACHE	acute physiology and chronic health evaluation
ASPEN	American Society for Parenteral and Enteral Nutrition
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CDI	<i>Clostridium difficile</i> infection
CFU	colony-forming units
CLP	cecal ligation and puncture
CRF	case report form
CUMC	Columbia University Medical Center
DNI	Do not intubate
DNR	Do not resuscitate
DCC	Data Coordinating Center
DSMC	data and safety monitoring committee
DSMO	data and safety monitoring officer
ECMO	extra-corporeal membrane oxygen
EDTA	ethylenediaminetetraacetic acid
EMR	electronic medical record
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
ER	emergency room
ESBL	extended-spectrum beta-lactamase
FDA	Food and Drug Administration
GCS	Glasgow coma scale
GI	gastrointestinal
GMP	good manufacturing practices
GRAS	generally recognized as safe
HRPO	human research protection office
IABP	intra-atrial balloon pump
ICD	International classification of diseases
ICU	intensive care unit
IND	investigational new drug
IQR	interquartile range
IRB	institutional review board
KPC	<i>Klebsiella pneumonia</i> carbapenemase
LAR	legally authorized representative
LDA	least discriminant analysis
LEfSe	linear discriminant analysis effect size

LPS	lipo-polysaccharide
MDR	multidrug resistant
MDRO	multidrug resistant organism
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NHSN	National Health and Safety Network
OR	operating room
ORP	Office of Research Protections
OTU	operational taxonomic unit
PCR	polymerase chain reaction
PI	primary investigator
PICRUST	phylogenetic investigation of communities by reconstruction of unobserved states
PPIs	proton pump inhibitors
PRMRP	peer-reviewed military research projects
QIIME	Quantitative Insights Into Microbial Ecology
qPCR	quantitative polymerase chain reaction
REDCap	Research Electronic Data Capture
rRNA	ribosomal ribonucleic acid
RT-PCR	real-time polymerase chain reaction
SAE	serious adverse event
SCFA	short-chain fatty acids
SD	standard deviation
SAPS3	simplified acute physiology score-3
SIRS	systemic inflammatory response syndrome
SOFA	sequential organ failure assessment
TNF	tumor necrosis factor
USAMRMC	U.S. Army Medical Research and Materiel Command
VRE	vancomycin-resistant <i>Enterococcus</i>
WGS	whole genome sequencing

Appendix 9.3

Columbia University Human Subjects Protocol Data Sheet

General Information

Protocol:	AAAS2576(M00Y03)	Protocol Status:	Approved
Effective Date:	03/17/2021	Expiration Date:	03/16/2022
Originating Department Code:		Medicine (751800X)	
Principal Investigator:		Freedberg, Daniel (def2004)	
From what Columbia campus does this research originate:		Medical Center	
Title:	Inulin the ICU		
Protocol Version #:	1	Abbreviated Title:	Inulin in the ICU
Was this protocol previously assigned a number by an IRB:			No

Is the purpose of this submission to obtain a "Not Human Subjects Research" determination?
No

Renewal Information

Enrollment status:

Open to enrollment or ongoing review of records/specimens

Provide any additional information necessary to explain the study status:

Ongoing enrollment, no changes to the study

Since the last renewal:

Have there been any changes in the relevant literature that would affect the study design or procedures?

No

Have there been any interim findings associated with this study?

No

Have there been any publications resulting from this study?

No

Have any participants been enrolled using the Short Form process?

No

Is there a Data Monitoring Committee (DMC), Data Safety Monitoring Board (DSMB), or other monitoring entity for this study?

Yes

Is the most recent report attached as part of this submission?

Yes

Is an annual Progress Report required by the funding organization or coordinating center for this study?

Yes

Is the most recent report attached as part of this submission?

Yes

Does this submission include a modification?

No

Has the consent form been revised in this submission?

No

Does this submission include a report of a protocol violation?

No

Attributes

Special review type: Check all that apply or check "None of the Above" box.

- ☐ Review for 45 CFR 46.118 Determination (involvement of human subjects is anticipated but is not yet defined)
- ☐ Funding review for Administrative IRB approval (such as for Center or Training Grants)
- ☒ None of the above

IRB of record information: Will a Columbia IRB be the IRB that is responsible for providing review, approval, and oversight for this study?

Yes

Select the most appropriate response:

Columbia will be the IRB of record for the study procedures conducted by Columbia researchers (Note: this response will apply to most submissions).

Is this research part of a multicenter study?

No

Please indicate if any of the following University resources are utilized:

- ☐ Cancer Center Clinical Protocol Data Management Compliance Core (CPDM)
- ☐ CTSA-Irving Institute Clinical Research Resource (CRR)
- ☐ CTSA- Irving Institute Columbia Community Partnership for Health (CCPH)
- ☒ None of the above

Background

Abbreviated Submission:

The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives.

If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Study Purpose and Rationale:

Provide pertinent background description with references that are related to the need to conduct this study. If this is a clinical trial, the background should include both preclinical and clinical data. Be brief and to the point.

- ☐ Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Note to the IRB on the inulin-COVID substudy In light of the COVID-19 pandemic, we are modifying this study protocol to create a COVID substudy. The following changes will be implemented for the COVID inulin substudy. Newly hospitalized (within 72

hours) patients 18 years old or more will be considered for enrollment if they test COVID+ and are receiving intravenous broad-spectrum antibiotics. Exclusion criteria will remain the same. Because of safety concerns and restrictions to direct access to patients, patients will be approached for consent remotely by telephone or WebEx so that study personnel only enters the room after the patient has given verbal consent. After verbal consent is obtained in the patient's room, the patient will sign standard print consent forms which will be placed in a clear ziplock plastic bag with the signature page upright. Before it is taken from the room, the bag will be wiped with bleach wipes to decontaminate it, soaking the exterior surfaces for >30 seconds on each side. Outside the room, this bag will then be placed into a second ziplock bag. If a surrogate gives consent and is on quarantine, faxed consent forms will be used to avoid face-to-face contact with the surrogate. After consent is obtained, samples will be collected and placed directly into freezer-safe containers containing EPA-approved viral inactivation media. Samples will be triple bagged for transport to the freezer facility by appropriately trained personnel. Other than as described above, the study approach to enrollment, intervention, and assessments will be identical to the main protocol. The main protocol and COVID substudy will be separately analyzed when the studies are complete.

Study Purpose and Rationale Multidrug resistant (MDR) infections are the leading cause of death in the intensive care unit (ICU) with mortality as high as 9 for every 100 patients admitted.¹ The bacteria and plasmids that encode antibiotic resistance reside in the human gut and prevent MDRO colonization. With antibiotics and other treatments received during critical illness, this protection is lost. New data show that there are specific "good" bacteria that combat colonization. Of these, the best data is for short chain fatty acid (SCFA)-producing colonic anaerobes. To understand the relationship between SCFA producers and colonization in the ICU, we have built two observational cohorts totaling over 500 Columbia ICU patients.²⁻⁴ In these patients, levels of SCFA-producing bacteria declined 5- to 10-fold during the 72 hours after ICU admission, with a 22% concurrent rise in prevalence of MDROs⁴ and a 50% increased risk for subsequent death or infection.³ The prebiotic fiber inulin is a vegetable-derived polysaccharide that appears to restore gastrointestinal colonization resistance against MDROs in animals and ambulatory humans. Inulin is safe in ambulatory patients⁵⁻¹³ with biologic effects seen at 16 g/day.¹⁴ In the ICU, inulin-type soluble fibers have been given up to 36 g/day without adverse events.¹⁵ This protocol hypothesizes that inulin supplementation in ICU patients will result in higher levels of SCFA-producing bacteria, decreased gut MDRO colonization, and lower risk for ICU-acquired MDR infections. To test this hypothesis, we will conduct a double-blind randomized clinical trial of inulin in 90 newly admitted medical ICU adults who meet sepsis criteria. Enrolled adults will receive 1:1:1 inulin 16 g/day, inulin 32 g/day, or placebo in divided doses for 7 days in the ICU and will provide serial rectal swabs, fecal samples, and clinical data for up to 30 days of active follow-up.

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Study Design:

Describe the methodology that will be used in this study, covering such factors as retrospective vs. prospective data collection, interventional vs. non-interventional, randomized vs. non-randomized, observational, experimental, ethnography, etc.

[] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

This will be a double-blind, randomized, placebo-controlled trial with two doses. In general, eligible subjects will be newly admitted medical ICU patients 18 years old with sepsis as defined by Sepsis-3 criteria who are receiving broad-spectrum antibiotics at the time of enrollment. Block randomization (blocks of 4) will be performed with 1:1:1 random computer allocation of subjects to inulin vs placebo. **Population** A total of 90 patients will be enrolled who complete both the baseline and Day 3 samples. If there are participant who are randomized but do not complete the Day 3 sample (e.g., because they die or decline to continue in the study) an additional participant will be enrolled to take their place. Participants will meet the following inclusion criteria: (1) hospitalized in a Columbia medical ICU, (2) 18 or more years old, (3) with sepsis, defined according to Sepsis-3

criteria, (4) on broad spectrum antibiotics, either ordered or received within the preceding 24 hours, (5) able to complete enrollment within 4 hours of ICU admission. The following are the exclusion criteria: (1) inability to receive oral or enteric fluids, (2) inulin allergy (exceedingly rare), (3) hyponatremia with serum sodium < 128 mEq/L because the intervention comes with a small amount of free water, (4) immunosuppression, defined as CD4 count <200 cells/mm³, neutrophil count <500 cells/mm³, or reasonable expectation that either CD4 count or neutrophils will fall below these levels during the 7 day study intervention period, (5) surgery on the intestinal lumen within 30 days, because such patients may have poor fiber tolerance, (6) DNR/DNI status, (7) lack of capacity and no legally authorized representative.

COVID sub-study: Newly hospitalized (within 72 hours) patients 18 years old or more will be considered for enrollment if they test COVID+ and are receiving intravenous broad-spectrum antibiotics. Exclusion criteria will remain the same. Intervention

In the active study arms, chicory root-derived inulin (Cargill Inc., Wayzata, MN) will be diluted in 250 ml of sterile water and given at 16 g or 32 g/day in 2 divided daily doses. The placebo arm will receive the same volume of sterile water twice daily. The intervention will be given for 7 days or until death or hospital discharge (continued on the floor, if necessary). Subjects, investigators and the treating ICU team will be blinded to the intervention arm. The intervention will be taken orally or given with enteric feeding by nursing staff overseen by the study team, with the first dose administered within 6 hours of ICU admission. **Intervention Dose** In the ambulatory setting, inulin impacts SCFA producer levels at doses of 12 to 16 g/day, with corresponding biologic effects relevant for ICU patients (e.g., decreases in serum LPS and CRP).^{14,17} Approximately 16 g/day therefore represents the minimum dose at which an effect *might* be seen; this was selected for the low dose arm of the study. However, patients in these ambulatory studies were not critically ill and did not receive antibiotics. It is possible that inulin will have lesser effects in the ICU compared to the ambulatory setting, and logical to test higher doses. To select a maximum study dose, we referenced our own experience with dietary fiber in the prospective cohort and published tolerability data from ICU studies of inulin-like prebiotic fiber. In our prospective ICU cohort, 30 g/day was the maximum observed dose of dietary fiber, and was not associated with any intolerance. In published literature, O'Keefe *et al.* reported tolerance up to a maximum of 36 g/day wheat dextran in the ICU.¹⁵ We therefore selected 32 g/day for the high dose study arm because it lies between these values and is exactly double a dose with proven biologic activity.

Assessments Samples will be gathered and bedside assessments made at day 0/baseline, 3 days, 7 days, 14 days, and 30 days. Primary analyses will use the baseline and Day 3 assessments. The additional samples will (1) test whether effects can be extended through 7 days (Day 7 samples), (2) test durability of effects (Day 14 and 30 samples), and (3) allow visualization of time-series data. At each time point, the following samples and data will be gathered: rectal swabs, spontaneous whole stools, urine, residual blood, and clinical data. At 3 and 6 months after ICU discharge, a telephone follow-up phone call will be made to gather clinical information and assess long-term outcomes.

Outcomes The study will compare the inulin vs placebo groups to accomplish 3 aims: (1) to determine the impact of inulin on SCFA producers in the ICU, (2) to determine the impact of inulin on gut colonization with MDR bacteria in the ICU, and (3) to determine the impact of inulin on delivery of nutrition in the ICU.

REFERENCES:

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Statistical Procedures:

Provide sufficient details so that the adequacy of the statistical procedures can be evaluated including power calculations to justify the number of participants to be enrolled into the study. Definitions of subject terms such as enrolled and accrued as used for Rascal submissions can be found in the Subjects section.

[] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

The overall aims are (1) understand the effects of inulin on the “good” or commensal bacteria and the overall dynamics of the microbiome in the ICU, (2) understand the effects of inulin on “bad” bacteria focusing on MDR organisms, and (3) understand the impact (if any) of inulin on the delivery of nutrition in the ICU. **Primary outcome.** The primary outcome will be determined by testing for a difference in ICU Day 3 SCFA producer levels, comparing any one inulin group to the placebo group. SCFA producer levels will be the proportion of reads assigned to producers of the SCFA butyrate as measured by whole genome sequencing of Day 3 rectal swabs. (This refers to sequencing of the bacterial genome, and no human sequencing will be done as part of this study.) Under this Aim, comprehensive “multi-omic” analyses will be conducted from rectal swabs, urine, blood, and stool to understand the dynamics of the microbiome, the effects of inulin, and the effects of other ICU interventions (e.g., antibiotics, opioids). A modified intention-to-treat approach will be used with subjects who receive 1 or more doses of the intervention analyzed under this approach. The study has been powered to detect a difference in SCFA producer levels that is similar to the observed difference in SCFA producer levels from our prospective ICU cohort. The rationale for this is that inulin must be at least as impactful as mixed dietary fiber to be a viable therapeutic. The proposed sample size of 30:30:30 will yield 80% power to detect a minimum difference of 0.32 standard deviations (SD) of within-individual change in SCFA producer levels, using an F-test with 0.05 significance level. In addition, the sample size will yield 80% power to detect a difference of 0.63 SD comparing any one inulin arm to the placebo arm using a two-sided t-test with 0.05 significance level and assuming equal variance. If the inulin arms have similar changes in SCFA producer levels, they will be combined and the study would have 80% power to detect a minimum 0.55 SD for inulin compared to placebo at the .05 significance level. **COVID sub-study:** The main protocol and COVID sub-study will be separately analyzed when the studies are complete. **Additional outcomes.** Aim 2 of the study will test for a difference in ICU Day 3 MDRO colonization status, comparing any one inulin group to the placebo group. MDRO colonization will be classified categorically (colonized vs not colonized) based on the results of culture for VRE, MRSA, and MDR Gram negatives. VRE and MRSA will be defined as present if they grow on selective (i.e., antibiotic-impregnated) media. MDR Gram negatives will be defined as present if they grow on MacConkey agar and show non-susceptibility to ceftriaxone using

standard cut-offs. Aim 3 of the study will test for a difference in the ICU Day 3 proportion of goal calories consumed, comparing any one inulin group to the placebo group. Goal calories consumed will be defined as the observed calories delivered divided by the patient-specific caloric requirement estimates which will be generated by a dietician using the Mifflin St. Jeor equation with the Penn State modification.

Exempt and Expedited

Is the purpose of this submission to obtain an exemption determination, in accordance with 45CFR46.101(b):

No

Is the purpose of this submission to seek expedited review , as per the federal categories referenced in 45CFR46.110?

No

Funding

Is there any external funding or support that is applied for or awarded, or are you the recipient of a gift, for this project?

Yes

Award Type	Funding Source Name	Name of awarding agency	Status	Award # or Application Date	Federal/State /Local Government Direct or Subcontract	What is the award covering?	Rascal PT Number
Federal/State/ Local Government	DoD PRMRP CTA	Department of Defense	Awarded/Received	PR181960	Direct Recipient: No Subcontract Sites	Entire Protocol	PT-AABO7879

Locations

Location Type	Facility Name	Domestic or International	Geographic Location	Local IRB Ethics Approval	Local Site Approval
NewYork-Presbyterian Hospital @ Columbia	Allen Pavilion ICU (Allen 2RE, 5141 Broadway)				
Columbia/CUMC	Mailman School, Rosenstein 7: Columbia Data Coordinating Center				
NewYork-Presbyterian Hospital @ Columbia	Milstein 3 MICA, MICB: enrollment of subjects				

Location Type	Facility Name	Domestic or International	Geographic Location	Local IRB Ethics Approval	Local Site Approval
NewYork-Presbyterian Hospital @ Columbia	Neurological ICU (Milstein 8th floor Garden South)				
Columbia/CUMC	P&S 3-401: analysis of data in PI's office				
Columbia/CUMC	P&S 8: storage of samples in PI's freezer unit				
Columbia/CUMC	P&S 9: processing of samples in Department of Medicine Microbiome Core Lab				

Personnel

UNI/Phone	Name	Role	Department	Edit/View	Obtaining Informed Consent
def2004 857-998-9370	Freedberg, Daniel	Principal Investigator	MED Digestive & Liver Diseases (751870X)	Edit	Y
Roles and Experience: Dr. Freedberg is the PI on the study and has extensive human subjects experience, including several years of experience enrolling ICU patients.					
el2888 412-779-8369	Lynch, Elissa	Other Engaged Personnel	MED Digestive & Liver Diseases (751870X)	Edit	Y
Roles and Experience: Clinical Research Nurse working with the PI and former NYP-Columbia RN.					
ep2681 212-305-4837	Poptanich, Erin	Non-Engaged Personnel	PAT Pathology (753800X)	View	N
Roles and Experience: CALM Lab member who will be helping with retrieval of left over blood samples.					
jn355 212-305-4837	Netterwald, Jane	Non-Engaged Personnel	PAT Pathology (753800X)	View	N
Roles and Experience: CALM Lab member who will be helping with retrieval of left over blood samples.					
rmw2126 443-857-0421	Wahab, Romina	Investigator	MED Pulmonary (751960X)	View	N
Roles and Experience: Dr. Wahab is an ICU physician with over 5 years in independent practice. She is permanently based at the Allen ICU (AICU) so we are adding her to the study personnel so that we have an on-site person at AICU if any issues arise and Dr. Freedberg cannot come up.					
sdl2134 541-729-3888	Leeds, Samantha	Other Engaged Personnel	MED Digestive & Liver Diseases (751870X)	View	N
Roles and Experience: Clinical Research Nurse who has worked in the Division of Digestive and Liver Diseases for several years. She will serve as a "back-up" for Elissa Lynch and help to collect samples and data on people already enrolled. But she won't enroll anyone new.					

Training and COI

The PI must ensure that each individual that is added as personnel has met the training requirements for this study (<http://www.cumc.columbia.edu/dept/irb/education/index.html>). For help identifying which research compliance trainings you may be required to take, visit the [Research Compliance Training Finder](#).



UNI	Name	COI	HIPAA	HSP (CITI)	Research with Minors (CITI)	FDA-Regulated Research (CITI)	S-I	CRC	Good Clinical Practice (GCP)	GCP - Third-party tracking	GCP Refresher	Genetic Research Consent
def2004	Freedberg, Daniel	09/14/2020	02/28/2011	01/06/2020	05/02/2014	01/06/2020	03/23/2020		01/06/2020			
el2888	Lynch, Elissa	07/14/2020	08/07/2019	08/07/2019		08/16/2019	08/07/2019	04/29/2020				
ep2681	Poptanich, Erin	10/12/2020	12/18/2017	01/11/2021	12/18/2017	12/18/2017	12/19/2017	12/20/2017	01/11/2021			
jn355	Netterwald, Jane	08/18/2020	04/02/2013	11/07/2019	11/07/2019	11/07/2019		08/21/2014	12/11/2019			
rmw2126	Wahab, Romina	06/08/2020	05/25/2009	12/03/2019	07/24/2020	07/24/2020			10/28/2020			
sdl2134	Leeds, Samantha	04/01/2020	07/07/2017		07/07/2017	07/07/2017		08/07/2017				

Departmental Approvers

Electronic Signature: Daniel Freedberg (751870X) -
Principal Investigator

Date: 03/04/2021

Privacy & Data Security

Indicate the methods by which data/research records will be maintained or stored (select all that apply):

☐ Hardcopy (i.e., paper)

☒ Electronic

Where will the data be stored?

Y

☐ On a System

☒ On an Endpoint

Identify what type of endpoint will be used (select all that apply):

☒ Desktop Computer

☐ Laptop Computer

☐ Mobile Device

☐ Other

Does this study involve the receipt or collection of Sensitive Data?

Yes

If any Sensitive Data is lost or stolen as part of your research protocol, you must inform both the IRB and the appropriate IT Security Office (CUMC IT Security if at CUMC; CUIT if at any other University campus).

What type of Sensitive Data will be obtained or collected? Select all that apply:

☐ Personally Identifiable Information (PII), including Social Security Numbers (SSN)



Will Social Security Numbers (SSNs) be collected for any purpose?

☒ Protected Health Information (PHI), including a Limited Data Set (LDS)

If any PHI is lost or stolen, you must inform both the IRB and the Office of HIPAA Compliance.

Indicate plans for secure storage of electronic sensitive data: check all that apply

☐ Sensitive data will not be stored in electronic format

☐ Sensitive data will be stored on a multi-user system

☒ Sensitive data will be stored on an encrypted endpoint

By Selecting an Endpoint Device and approving this protocol for submission to the IRB, the PI is attesting that the device and any removable media that may be used have been or will be registered and/or will be maintained in compliance with the University's Information Security Charter and all related policies. It is important that this information is updated, during the course of the study, as new devices are added.

Provide a description of how the confidentiality of study data will be ensured, addressing concerns or protections that specifically relate to the data storage elements identified above (e.g. hard copy, electronic, system, and/or endpoint):

Study data will be stored electronically or on paper CRFs in a coded form, and only the PI and the research study coordinator will have access to the linking file that provides the code. This password-protected linking file will contain MRNs (the only directly identifiable data that we will retrieve) and random alphanumeric identifiers. The main data file will not contain direct identifiers. Both files will be stored on encrypted Columbia endpoints.

If your project is not NIH funded, has a Certificate of Confidentiality (CoC) been requested for this research?

No

Provide a description of the protections in place to safeguard participants' privacy while information is being collected:

Information will be collected from the electronic medical record or by direct visualization of the participant. This information will be recorded electronically, and the safeguards for the security of this information are described above under the Data Security section. The only situation in which information will be collected by asking the participant questions is at the 3 and 6 month telephone follow-up interviews regarding overall health and functional status. These phone calls will be made from a locked private research office and we will begin by asking "are you in a place where you can speak privately?" in order to minimize the potential for loss of privacy while describing current health status. We recognize that privacy could potentially be compromised by compelled disclosure of research notes or by mandatory reporting.

Procedures

Is this project a clinical trial?

Yes

Is this project a clinical trial that requires registration with www.clinicaltrials.gov?

Yes

Has this study been registered with www.clinicaltrials.gov?

Yes

Please provide the registration number:

NCT03865706

Is this project associated with, or an extension of, an existing Rascal protocol?

No

Do study procedures involve any of the following?

Analysis of existing data and/or prospective record review

No

Audio and/or video recording of research subjects

No

Behavioral Intervention?

No

Biological specimens (collection or use of)

Yes

Cancer-related research

No

Drugs or Biologics

Yes

Future use of data and/or specimens

Yes

Genetic research

No

Home Visits

No

Human embryos or human embryonic stem cells

No

Imaging procedures or radiation

No

Medical Devices

No

Surgical procedures that would not otherwise be conducted or are beyond standard of care

No

Will any of the following qualitative research methods be used?

Survey/interview/questionnaire

Yes

NOTE: You must attach a PDF version of the survey(s)/interview(s)/questionnaire(s) to this protocol prior to submission.

Systematic observation of public or group behavior

No

Program evaluation

No

Will any of the following tests or evaluations be used?

Cognitive testing

No

Educational testing

No

Non-invasive physical measurements

No

Taste testing

No

Is there an external protocol that describes ALL procedures in this study?

No

Please describe ALL study procedures in detail.

NOTE: Be sure to detail all of the procedures above to which a "yes" response was selected. Also detail any additional procedures that may or may not fall into the categories listed above.

Study enrollment

Newly admitted ICU patients will be identified at the time of ICU bed allocation through the assistance of ICU personnel, a strategy we have used in past studies. This allows rapid identification of potential subjects so that they can be quickly reached for the intervention. After consultation with the treating ICU team, subjects who are thought by the medical team to be eligible will have the final, formal eligibility evaluation completed at the bedside. Subjects will only be approached after consent has been obtained from the attending physician of record (i.e., the ICU attending who is on duty). We anticipate that >50% of patients will lack decision-making capacity and will accept consent from a Legally Authorized Representative (LAR) acting as the patient's surrogate in these situations. This is a common approach in ICU trials and our other trials take the same approach.

Study assessments

Samples will be gathered and bedside assessments made at day 0/baseline, 3 days, 7 days, 14 days, and 30 days. Primary analyses will use the baseline and Day 3 assessments. The additional samples will (1) test whether effects can be extended through 7 days (Day 7 samples), (2) test durability of effects (Day 14 and 30 samples), and (3) allow visualization of time-series data. At each time point, the following samples and data will be gathered: rectal swabs, spontaneous whole stools, urine, residual blood, and clinical data. At 3 and 6 months after ICU discharge, a telephone follow-up phone call will be made to gather clinical information and assess long-term outcomes. Biologic samples are described below. For the clinical data gathered, case report forms for each study assessment will be completed which document adverse events, long-term origin (e.g., nursing home), short-term origin (e.g., hospital floor), the Glasgow Coma Scale (GCS), the use of life support devices including mechanical ventilation, hemodialysis, or additional life-support devices such as extra-corporeal membrane oxygen (ECMO) or an intra-atrial balloon pump (IABP); and the presence or absence of intravenous lines or catheters including a central venous catheter, urinary catheter, arterial catheter, nasal or oral gastric tube, or rectal tube. Using duplicate data entry, anonymized CRF data will be transferred into a secure REDCap database custom-designed for the trial by the CUMC Data Coordinating Center. Additional variables will be entered directly into REDCap including the component variables of the SOFA score and measures related to nutritional intake. At 3 and 6 months, telephone interviews will be conducted with subjects or their surrogates to ascertain vital status (1) discharge location type (home, short-term rehabilitation, or long-term rehabilitation), (2) hospital admission or physician office visits after ICU discharge, (3) infections or other adverse events after ICU discharge. If there are non-CUMC healthcare interactions, permission will be requested to obtain relevant records. Among surviving subjects, the EQ-5D-5L (EuroQol 2009) and Katz' Index of Independence in ADLs (Activities of Daily Living) will be used to determine function.

COVID sub-study:

Samples will be collected and placed directly into freezer-safe containers containing EPA-approved viral inactivation media. Samples will be triple bagged for transport to the freezer facility by appropriately trained personnel.

Biological Specimens

Add an individual entry for each human specimen type that will be collected or utilized for the proposed study.

For each specimen type, indicate the source or sources from which you will obtain the specimens.

The use of specimens for research purposes may require that informed consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) be obtained from subjects.

Type:

Stool

Source:

☒ From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia

Select all that apply to this specimen type:

☐ Specimens will be prospectively collected specifically for this research.

☒ Residual specimens from clinical care that would otherwise be discarded have been or will be collected.

☐ Specimens to be analyzed will be (or have been) collected from a commercial source.

☐ Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.

☐ From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia

Description of Specimen and Method of Obtaining:

At each study assessment, the study team will work with nurses to gather the first stool produced after each study assessment. In ICU patients, these stools are routinely gathered using a bedpan and then discarded. The study team will intercept the stools prior to discard and scoop out an 8 g aliquot.

Indicate the manner in which the specimens will be labeled:

☐ Specimens will be labeled with direct identifiers

☒ Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier

☐ The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain

☐ Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of this Rascal submission.

Type:

Blood

Source:

☒ From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia

Select all that apply to this specimen type:

☐ Specimens will be prospectively collected specifically for this research.

☒ Residual specimens from clinical care that would otherwise be discarded have been or will be collected.

☐ Specimens to be analyzed will be (or have been) collected from a commercial source.

☐ Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.

☐ From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia

Description of Specimen and Method of Obtaining:

At each study assessment, the study team will work with the CALM laboratory to obtain leftover clinical blood samples for future analyses. We will collect no more than 6 mL of residual blood from a yellow-top tube and no more than 4 mL of residual blood from a lavender-top (EDTA) tube. There will be no blood draws as part of this study.

Indicate the manner in which the specimens will be labeled:

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- ☐ Specimens will be labeled with direct identifiers
- ☒ Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier
- ☐ The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain
- ☐ Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of this Rascal submission.

Type:

Urine

Source:

- ☒ From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia

Select all that apply to this specimen type:

- ☒ Specimens will be prospectively collected specifically for this research.
- ☐ Residual specimens from clinical care that would otherwise be discarded have been or will be collected.
- ☐ Specimens to be analyzed will be (or have been) collected from a commercial source.
- ☐ Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.
- ☐ From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia

Description of Specimen and Method of Obtaining:

At each study assessment, 15 mL of freely voided or catheterized urine will be gathered.

Indicate the manner in which the specimens will be labeled:

- ☐ Specimens will be labeled with direct identifiers
- ☒ Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier
- ☐ The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain
- ☐ Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of this Rascal submission.

Type:

Other

Rectal swab

The Anatomic Pathology approval request form and guidance on requirements to attach the form can be found on the HRPO website, in the "Biospecimen Research" section of the Human Research Policy Guide page: <https://research.columbia.edu/human-research-policy-guide>

Source:

- ☒ From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia

Select all that apply to this specimen type:

- ☒ Specimens will be prospectively collected specifically for this research.

- ☐ Residual specimens from clinical care that would otherwise be discarded have been or will be collected.
- ☐ Specimens to be analyzed will be (or have been) collected from a commercial source.
- ☐ Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.
- ☐ From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia

Description of Specimen and Method of Obtaining:

At each study assessment, duplicate flocked nylon swabs (Copan Diagnostics) will be performed with the patient in the left lateral decubitus position. These soft swabs are gently rubbed against the anal canal to gather fecal debris.

Indicate the manner in which the specimens will be labeled:

- ☐ Specimens will be labeled with direct identifiers
- ☒ Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier
- ☐ The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain
- ☐ Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of this Rascal submission.

Drugs/Biologics

On the General Information page you have indicated that the protocol version associated with the use of this drug/biologic is as follows: 1

Please note that a Protocol Version # is required for protocols using a drug or biologic, and you will not be allowed to submit this protocol until the Protocol Version # field is complete. Please ensure that the Protocol Version # is completely and accurately reported on the General Information page.

List each drug or biologic that will be administered as the object of the protocol or is being used because it is relevant to the aims of the research protocol. This applies whether the drug/biologic is not yet FDA-approved (i.e., is investigational), is FDA approved and used in accordance with its labeling, or is an approved product that is being used in an investigational manner (i.e., off-label use is being studied).

Note that the questions apply only to drugs used in clinical investigations. Emergency use of a drug that is not yet FDA-approved is not a clinical investigation, and a submission in Rascal may not be required. Please contact the IRB for assistance if emergency use of a drug or biologic that is not yet FDA-approved is being considered: (212) 305-5883.

Name:

Chicory root-derived inulin in 250 mL sterile water

Dose:

16g/day or 32g/day in 2 divided doses

Study phase:

Phase 2

Manufacturer Information

Name: Cargill, Inc.
Address: 15407 McGinty Road West, Wayzata, MN 55391
Contact information: Cargill Inc. - 800-227-4455

Route of administration:

Oral

Is the drug/biologic FDA-approved and used in accordance with its labeling?

No

Select a category:

Not FDA-approved

Does the Use of the drug/biologic require an Investigational New Drug (IND) or Biological IND (BB-IND) application?

Yes

Select status of IND:

Accepted (e.g. IND# issued)

Provide IND#:

137359

Select type of IND holder:

Columbia University Faculty

Please note that the following documents will be required prior to final approval of this protocol:

- Most recent protocol submitted to the FDA (required before IRB review)
- FDA Form 1571
- FDA Form 1572
- FDA acknowledgment letter or FDA "Safe to Proceed" documentation, including the conditional approval letter if one has been received
- Form of Notice by CU Faculty IND/IDE Holder

Please describe how the responsibilities of the IND holder, who is considered per FDA regulations to be the sponsor, will be met. Elements to be included are described in the Help Text. If all elements are in an attached stand-alone protocol, please so indicate by selecting that statement below, in which case, entry in the text box is not required.

[x] Plans to address Sponsor requirements - IRB approval, monitoring, compliance with the IRB-approved protocol, evaluating safety and efficacy, recordkeeping, submitting amendments, IND Safety Reports and Annual Reports to the FDA, and submitting required reports to the IRB - are in the attached stand-alone protocol.

IND/BB-IND holder name:

Julian Abrams and Daniel Freedberg

IND/BB-IND holder address:

Columbia University Medical Center, 630 WEST 168TH STREET, P&S 3-401, New York, NY 10032

IND/BB-IND holder contact info:

Daniel Freedberg 212-342-3302

Will the drug/biologic be dispensed by the CUMC Research Pharmacy, which is responsible for the storage, handling, accountability, and dispensing of investigational drugs to research investigators? CUMC Research Pharmacy policy: <https://researchpharmacy.cumc.columbia.edu/policies.html>

Yes, I confirm the drug will be dispensed by the Research Pharmacy

Future Use

For what materials do you anticipate future research use? Select all that apply.

☒ Data

☒ Biological Specimens

Please indicate how data and/or specimens will be retained for future use:

☒ Some or all data and/or specimens, as applicable, will be retained by Columbia researchers for future use.

How are the materials intended to be used for research in the future?

Current PI will retain the materials and there is no intent to create a repository or share with other CU researchers. Note: Information provided in original consent forms will be considered when an addition of future uses is submitted via modification.

What future uses are anticipated?

Spin-off studies using samples and data are likely, to appropriately follow-up on the findings of this trial. All future use of samples and data will involve de-identified materials - only the PI will have access to identifiers.

How will the data and/or specimens, as applicable, be labeled during storage for future uses.

☒ In the same manner as during collection (e.g., with direct identifiers, coded, de-identified, anonymous)

☐ In a different manner than during collection. Select all that apply:

Describe the physical storage for the specimens/data, including location.

☒ In the same manner as during collection

☐ In a different manner than during collection

Describe who will have access to the stored data and/or specimens.

Only the PI will have access to data/specimens at this time. He will share them with appropriate future researchers depending on the results of the trial.

☒ Some or all data/specimens will be released to a non-Columbia entity for future use and Columbia researchers will not have direct control.

Indicate to whom the data/specimens will be released

☐ Sponsor

☐ Non-Columbia repository

☒ Other

Describe

Collaborative researchers.

Describe plans for release of data and/or specimens.

We anticipate the possibility of future research collaborations outside of Columbia, depending on the results of the trial and the availability of expertise.

Recruitment And Consent

Recruitment:

Will you obtain information or biospecimens for purposes of screening or determining eligibility?

Yes

Select one of the following:

The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

Describe plans for screening and/or determining eligibility of prospective subjects:

During screening, investigators will work with the ICU team and look at the EMR of ICU patients in order to determine eligibility. No data will be retained during this screening process.

Describe how participants will be recruited:

The ICUs at Columbia are “open” units which means that all of the patients in the ICU are under the care of the ICU attending at that time. Within these units, we will identify potentially eligible patients at the time of ICU admission by working with unit coordinators who are aware of new admissions at the time of bed assignment (i.e., slightly before the patient is actually transferred into that ICU bed). At this time there are plans to do this on weekdays only and during standard business hours. After prescreening patients for eligibility against the inclusion/exclusion criteria through the unit coordinators, we will ask the ICU attending if he or she feels that the patient is appropriate for the study and, if so, if they would provide the patient/surrogate with information about the study (default) or, if not, if they would ask the patient/surrogate if we can approach them and, if yes, document this. We will always check with the ICU attending before approaching the patient. We anticipate that >50% of patients will lack decision-making capacity and we will consent from a surrogate in these situations, with the surrogate providing written (signed) informed consent. Surrogates who are not available at the ICU bedside immediately will be contacted by telephone and either asked to meet at the bedside or sent a facsimile copy of the consent form to review and return if they are not in the area. The surrogate (or the subject if he or she regains capacity) will have the ability to withdraw at any time. Issues related to altered capacity, privacy and time for decision-making, consent of LARs, and ongoing consent are discussed in detail below. Once ICU permission has been obtained and eligibility criteria have been met, the patient or surrogate will be approached regarding the study at the earliest possible moment that is appropriate clinically and preserves privacy.

COVID sub-study:

Because of safety concerns and restrictions to direct access to patients, patients will be approached for consent remotely by telephone or WebEx so that study personnel only enters the room after the patient has given verbal consent. After verbal consent is obtained in the patient’s room, the patient will sign standard print consent forms which will be placed in a clear ziplock plastic bag with the signature page upright. Before it is taken from the room, the bag will be wiped with bleach wipes to decontaminate it, soaking the exterior surfaces for >30 seconds on each side. Outside the room, this bag will then be placed into a second ziplock bag. If a surrogate gives consent and is on quarantine, faxed consent forms will be used to avoid face-to-face contact with the surrogate. When patients are enrolled, the date and time of enrollment will be entered into the research record and documented on the consent form.

Select all methods by which participants will be recruited:

- ☐ Study does not involve recruitment procedures
- ☒ Person to Person
- ☐ Radio
- ☐ Newspapers
- ☐ Direct Mail
- ☐ Website
- ☐ Email
- ☐ Television
- ☐ Telephone
- ☐ Flyer/Handout
- ☐ Newsletter/Magazine/Journal
- ☐ ResearchMatch
- ☐ CUMC RecruitMe

Additional Study Information: Please add a description of your study as you would like it to be

displayed on the RecruitMe website.

Informed Consent Process:

Informed Consent Process, Waiver or Exemption: Select all that apply

☒ Informed consent with written documentation will be obtained from the research participant or appropriate representative.

Documentation of informed consent is applicable to:

The study in its entirety

Identify the portion of the study (e.g., prospective portion, focus groups, substudy 2) or subject population for which documentation of consent will be obtained::

Subjects with capacity or LARs who are physically present at the bedside.

Documentation of participation will be obtained from::

☒ Adult participants

☐ Parent/Guardian providing permission for a child's involvement

☒ Legally Authorized Representatives (LARs)

Describe how participants' written consent will be obtained:

Study personnel will concisely describe the study and what it involves. The consent form will be given to subjects or surrogates in a manner such that they have the opportunity to review it carefully and discuss the information provided.

For any illiterate subjects or surrogates, the study will be briefly described and the consent form will be read verbatim. The information presented will be easily understandable to laypeople regardless of education level but will be sufficiently detailed such that the entire study and its aims are comprehensible.

☐ Informed consent will be obtained but a waiver of written documentation of consent (i.e., agreement to participate in the research without a signature on a consent document) is requested.

☐ A waiver of some or all elements of informed consent (45 CFR 46.116) is requested.

☐ Planned Emergency Research with an exception from informed consent as per 21 CFR 50.24.

☐ This is exempt research.

Subject Language

Enrollment of non-English speaking subjects is expected.

Languages anticipated:

Spanish

As you plan on enrolling non-English speaking subjects, administrative IRB approval of the translated documents (e.g., consent, recruitment materials, questionnaires) in the above selected

languages are required. Please see the IRB's policy on the Enrollment of Non-English Speaking Subjects in Research for further details

(<http://www.cumc.columbia.edu/dept/irb/policies/documents/Nonenglishspeakingsubjects.Revised.FINALDRAFT.111909.website.doc>).

Capacity to Provide Consent:

Do you anticipate using surrogate consent or is research being done in a population where capacity to consent may be questionable?

Yes

Who will be enrolled?

Those with and/or without capacity to provide their own consent (surrogate consent is proposed)

Describe the process that will be in place to identify an appropriate surrogate to provide consent:

In patients who lack capacity to give informed consent, the LAR who is acting as the patient's surrogate will be determined in accordance with New York State law as defined in the Family Health Care Decision Act. In brief, this law states that the procedure to determine the LAR who may act as surrogate is in the following order of priority: First, an individual who is designated as the representative or agent through a healthcare proxy that is properly executed. Second, if a designated surrogate does not exist, reasonably willing and competent people in the following order of priority: (A) the spouse (if not legally separated) or the domestic partner; (B) a son or daughter 18 years of age or older; (C) a parent; (D) a brother or sister 18 years of age or older; (E) a close friend (meaning a person 18 years of age or older who has maintained such regular contact with the subject as to be familiar with the subject's activities, health and beliefs). In practice, identification of surrogates is common in the ICU where patients frequently lack capacity and consent must be obtained for invasive procedures such as the intubation and mechanical ventilation or the placement of central venous lines.

Describe the plan to assess capacity both at the time of enrollment and, if applicable, throughout each subject's participation:

Assessment of capacity. Capacity will be assessed by the treating ICU team rather than study personnel, and study personnel will reference the ICU's determination of capacity. If there is any question of a possible change in decision-making capacity since the ICU team's assessment, the study team will directly confer with the ICU. The ICU's standard approach for assessment of capacity is that the patient (1) is able to communicate; (2) can understand their treatments and alternatives relating to their hospital care and participation in the proposed study or intervention (the patient must be able to repeat back in his/her own words an explanation of treatment plan or study, the risks involved, and the alternative to not participate); (3) can grasp that there are no consequences to declining the study; (4) has ability to reason (can express their goals and values in participating in a study that seeks to reduce risk for infections in patients like themselves).

Ongoing consent. When subjects have decision-making capacity, their willingness to participate in the study will be reassessed at each study visit by asking the question, "Do you wish to continue in the study?" Subjects who answer "No" will be immediately withdrawn from the study. When subjects do not have decision-making capacity, their surrogates will be provided with the investigators' telephone contact information at the time of initial consent and instructed that they should call at any time to withdraw subjects

from the study.

Ongoing assessment of capacity. All subjects with surrogate consent will be assessed for capacity throughout the rest of their hospital stay at each study visit. If these subjects regain capacity, they will consent or decline to continue to participate at that time. Again, the ICU team's determination of capacity will be utilized, and the ICU team will be directly consulted if there is any question regarding a change in capacity. If subjects with surrogate consent never regain capacity by the time of discharge because of death or neurological disability, then surrogate consent will be accepted as final.

Research Aims & Abstracts

Research Question(s)/Hypothesis(es):

The overall aim of this study is to perform a randomized, double-blind trial of inulin versus placebo for the purpose of testing whether inulin prevents gastrointestinal colonization of multidrug-resistant bacteria. The specific hypotheses that will be tested are: (1) Inulin increases SCFA producers and fecal SCFA levels during critical illness; (2) Inulin decreases gut MDRO colonization and infection during critical illness; and (3) Inulin does not diminish caloric intake during critical illness and is well tolerated.

Scientific Abstract:

The gastrointestinal microbiome checks the expansion of pathogens through a process known as colonization resistance. Loss of colonization resistance permits the expansion of pathogens including vancomycin-resistant *Enterobacteriaceae* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and multidrug resistant (MDR) Gram negative bacteria and leads to subsequent infections with these and other difficult-to-treat MDR organisms. Nowhere is this more important than in the intensive care unit (ICU), where antibiotic-resistant infections are the leading cause of morbidity and mortality. Currently, there are no strategies designed to preserve colonization resistance in the ICU or similar at-risk settings, and this trial will test the use of a vegetable derived soluble fiber (inulin) for this purpose. Dietary fiber is the most important driver of gut microbiome composition in healthy individuals and is the primary fuel substrate for commensal colonic anaerobes. Fiber-metabolizing gastrointestinal bacteria generate short-chain fatty acids (SCFAs) which moderate colonic inflammation, contribute to the thickness of the colonic mucus layer, and directly resist enteric pathogens. Our preliminary data from critically ill adults suggest that depletion of fiber-metabolizing bacteria from the gut results in loss of colonization resistance. Ironically, standard practice is to minimize prebiotic fiber in the ICU based on the assumption that fiber will be poorly tolerated. We hypothesize that inulin will be well tolerated and will favorably alter gut microbiome colonization resistance even in the setting of antibiotics to decrease MDR pathogen colonization in the ICU. The *short-term objective* of this research is to test inulin in the ICU by randomization of 120 critically ill adults to 16 or 32 g/day inulin or placebo. The *long-term objective* of the research is to contribute to knowledge which will lead to the development of successful, gut microbiome-based strategies to prevent pathogen colonization and infection in the ICU. The results of these Aims will provide data in support of definitive subsequent trials. We believe that fiber is a novel and readily accessible therapy that can rapidly be translated into an intervention to reduce pathogen colonization and the spread of antibiotic resistant infections in the

Lay Abstract:

Trillions of bacteria coexist with humans, primarily within our gastrointestinal tracts. Normally, "good" gut bacteria have a symbiotic relationship with us and one of their main functions is to keep down disease-causing bacteria. This is particularly important in the intensive care unit (ICU), where normal bacteria are often depleted by antibiotics and where infections by disease-causing bacteria are very common and deadly. Prebiotic fiber is a major component of all plant-based foods and is the main fuel for gut bacteria. Studies show that, after antibiotics, how much fiber you eat is the most important controller of the types and amounts of bacteria that live inside you. Fiber is natural and is well tolerated and safe even in very sick patients. This study will test one type of fiber called inulin, which exists in large amounts in unprocessed chicory root, garlic, onions, and other vegetables. We already know that inulin promotes good bacteria in healthy volunteers. The goal of the study is to understand whether inulin will also promote good bacteria even in ICU patients who are getting antibiotics and many other powerful medical interventions. In this setting, are the good bacteria increased by inulin and do the bad bacteria diminish? Beyond testing inulin, we want to understand how bacteria interact in the ICU to cause health or disease so that in the future we can develop therapies (either inulin or other therapies) that will prevent ICU infections.

Risks, Benefits & Monitoring
Abbreviated Submission:

The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives. .

If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Potential Risks:

Provide information regarding all risks to participants that are directly related to participation in this protocol, including any potential for a breach of confidentiality. Risks associated with any of the items described in the Procedures section of this submission should be outlined here if they are not captured in a stand-alone protocol. Risks of procedures that individuals would be exposed to regardless of whether they choose to participate in this research need not be detailed in this section, unless evaluation of those risks is the focus of this research. When applicable, the likelihood of certain risks should be explained and data on risks that have been encountered in past studies should be provided.

☐ Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Foreseeable risks fall into three categories: (1) risks related to the study intervention, (2) risks related to the gathering of study samples, and (3) risks related to the privacy and confidentiality of data. (1) Risks related to the study intervention. Inulin has been studied extensively in ambulatory

patients or healthy volunteers where it has been safe. The main reported adverse effect is self-resolving bloating. A literature review identified a total of 12 published ICU-based trials of fiber tested alone or in combination including 1,295 subjects. Several studies tested inulin in combination with other fibers or in combination with probiotics (living bacteria) but no ICU studies tested inulin alone. The ICU trials of mixed fiber did not test fiber for the purpose of preventing pathogen colonization, but they did monitor carefully for adverse effects. In these trials, there were no adverse effects from fiber other than self-resolving abdominal distension and higher residual gastric volumes. Based on these data, the primary anticipated risk from fiber is bloating/abdominal distension which is expected to resolve without intervention. Tolerability will be carefully monitored as part of this study and will be an important consideration for future trials.

(2) Risks related to study samples. All of the study samples are minimally invasive. Specific risks are as follows: · *Flocked rectal swabs*. There is the potential risk for discomfort and embarrassment when the rectal swab is performed, for rectal irritation or minor trauma in the setting of preexisting peri-rectal pathology (e.g., hemorrhoids), or for problems related to turning the subject in subjects who lack the ability to turn themselves. · *Whole stools*. There is the potential risk for embarrassment related to fecal testing. · *Urine*. There is the potential risk for discomfort related to manipulation of urinary catheters or for embarrassment related to clean-catch voiding of urine. · *Venous blood*. Residual blood will be used so the only risk related to the blood sample is loss of privacy. (3) Risks related to the privacy and confidentiality of data. There is the potential for loss of privacy as a consequence for taking part in this study, both related to the collection/labelling of samples and related to the collection and storage of clinical data. Measures are in place to minimize these risks.

Potential Benefits:

Provide information regarding any anticipated benefits of participating in this research. There should be a rational description of why such benefits are expected based on current knowledge. If there is unlikely to be direct benefit to participants/subjects, describe benefits to society. Please note that elements of participation such as compensation, access to medical care, receiving study results, etc. are not considered benefits of research participation.

[] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

This study was not designed to directly benefit participants. Future ICU patients may benefit from the knowledge gained. There is no financial compensation for participating in the study.

Alternatives:

If this research involves an intervention that presents greater than minimal risk to participants, describe available alternative interventions and provide data to support their efficacy and/or availability. Note, participants always have the option not to participate in research.

[] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

There is no obligation to participate in this study and subjects/surrogates who do initially choose to participate can withdraw at any time. Participation or non-participation in the study will not alter patient care in any way, aside from receipt or non-receipt of the study intervention. We consider all ICU patients to be vulnerable because they are all critically ill. Accordingly, procedures are in place to minimize influence and coercion. Study staff will stress throughout the informed consent process that (1) the research team is not involved with the subject's care in any way and (2) that

the subject or surrogate may choose not to participate or may withdraw from the study at any time without explanation.

Data and Safety Monitoring:

Describe how data and safety will be monitored locally and, if this is a multi-center study, how data and safety will be monitored across sites as well.

☐ Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Daniel Brodie, the Director of Medical Intensive Care Units at our institution, will serve as the Data Safety Monitoring Officer (DSMO) and will oversee the study Data Safety Monitoring Board (DSMB). Before initiating research, the study will be registered on clinicaltrials.gov. Specific Adverse Events (AEs) have been pre-defined to ensure rigorous ascertainment (Aim 3). DSMB reports will be generated through REDCap, a secure, web-based data management system after 10, 20, 30, and 45 patients are enrolled. Toxicity monitoring will be performed using a frequentist approach at the same intervals. A complete Data and Safety Monitoring Plan (DSMP) is attached.

Subjects

Unless otherwise noted, the information entered in this section should reflect the number of subjects enrolled or accrued under the purview of Columbia researchers, whether at Columbia or elsewhere.

Target enrollment:

100

Number enrolled to date:

8

Number enrolled since the last renewal or, if this is the first renewal, since the initial approval:

8

Number anticipated to be enrolled in the next approval period:

15

Does this study involve screening/assessment procedures to determine subject eligibility?

No

Of the number of subjects enrolled, or the number accrued for interventional studies with a screening process:

How many remain on the study?

1

How many are off study?

7

How many completed the study?

6

Have any withdrawn of their own initiative?

No

Have any been removed by PI?

No

Have any been lost to follow-up?

No

Have any died while on study?

Yes

How many?

1

Please explain, including whether death was related to participation in this study:

The patient was enrolled but her clinical condition quickly deteriorated. The patient's death was unrelated to the study as she never received the intervention.

Have any subject complaints been received?

No

Is this a multi-center study?

No

Does this study have one or more components that apply to a subset of the overall study population (e.g. Phase 1/2, sub-studies)?

No

Of the number enrolled, or the number accrued for interventional studies with a screening process, indicate:

Population Gender

Females
37%

Males
63%

Non Specific
0%

Population Age

0-7	8-17	18-65	>65	Non Specific
0%	0%	75%	25%	0%

Population Race

American Indian/Alaskan Native	Asian	Native Hawaiian or Other Pacific Islander	Black or African American	White	More than One Race	Non-Specific
0%	0%	0%	0%	0%	0%	100%

Population Ethnicity

Hispanic or Latino	Not Hispanic or Latino	Non-Specific
0%	0%	100%

Vulnerable Populations as per 45 CFR 46:

Will children/minors be enrolled

No

Will pregnant women/fetuses/neonates be targeted for enrollment?

No

Will prisoners be targeted for enrollment?

No

Other Vulnerable Populations:

[x] Individuals lacking capacity to provide consent

Are the procedures this population will be exposed to minimal risk?

Yes

Please ensure that your plan for assessing capacity to provide consent is described on the Informed Consent page.

[] CU/NYPH Employees/Residents/Fellows/Interns/Students

[] Economically disadvantaged

☐ Educationally disadvantaged

☒ Non-English speaking

Please ensure that your plan to enroll subjects in their primary language is described on the Informed Consent page.

☒ Other Vulnerable populations

This is ICU research-based, and we believe that the ICU population is inherently vulnerable by virtue of being critically ill and totally dependent on care providers. Procedures are in place to make sure that this inherent vulnerability is not a major factor in the decision by a patient or surrogate regarding whether to participate.

☐ None of the Populations listed above will be targeted for Enrollment

Subject Population Justification:

The ICU population has been selected for this study because the ultimate aim of the study is to prevent the difficult-to-treat, antibiotic-resistant infections that arise most often in ICU patients.

Does this study involve compensation or reimbursement to subjects?

No

Attached Attestation

Principal Investigator	Date Created
Daniel Freedberg (def2004)	03/04/2021

Attached HIPAA Forms

Number	Type	Title	Status
AAAO7053	A	ICU Inulin Study Spanish	Approve
AAAO3920	A	Inulin in the ICU	Approve
AAAO6281	D	screening for inulin study	Approve

Attached Consent Forms

Number	Copied From	Form Type	Title	Active/InActive	Initiator
AABS4300	AABS4300	Consent	ICU inulin study - Consent Form	Inactive	Daniel Freedberg (def2004)

Documents

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	O:\dim2115's Profile\Project Files\Dr.Freedberg's projects\l	Certificate of Translation	Certification of Translation for Inulin CF Spanish July 19 2019.pdf	Y	No	07/19/2019	Dagmara Moscoso (dim2115)

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	Spanish Translation Certificate	Certificate of Translation	Certification of Translation personnel update August 26 2019.pdf	Y	No	08/26/2019	Dagmara Moscoso (dim2115)
No	Spanish CF personnel update	Consent Form/Addendum	AAAS2576 ICF Spanish personnel update August 26 2019.pdf	Y	No	08/26/2019	Dagmara Moscoso (dim2115)
No	E-consent REDCap PDF	Consent Form/Addendum	AAAS2576_econ sent_form.pdf	Y	No	05/29/2020	Elissa Lynch (el2888)
No	Consent form with modified format	Consent Form/Addendum	Inulin Consent Form 3.1.19.pdf	Y	No	03/01/2019	Daniel Freedberg (def2004)
No	updated CF July 10 2019	Consent Form/Addendum	Inulin Consent Form 7.10.19 clean copy.pdf	Y	No	07/11/2019	Dagmara Moscoso (dim2115)
No	English consent for Y1M5	Consent Form/Addendum	Inulin Consent Form 8.2.19 clean copy.pdf	Y	No	08/02/2019	Daniel Freedberg (def2004)
No	Inulin Consent Form English 2.20.20	Consent Form/Addendum	Inulin Consent Form English 2.20.20.pdf	Y	No	02/20/2020	Elissa Lynch (el2888)
No	Inulin Consent Form Spanish 2.20.20	Consent Form/Addendum	Inulin Consent Form Spanish 2.20.20.pdf	Y	No	02/20/2020	Elissa Lynch (el2888)
No	Inulin e-consent screenshots	Consent Form/Addendum	Inulin e-consent screenshots.pdf	Y	No	06/09/2020	Elissa Lynch (el2888)
No	Inulin COVID sub-study consent form	Consent Form/Addendum	Inulin-COVID sub-study consent form.pdf	Y	No	03/24/2020	Daniel Freedberg (def2004)
No	Inulin COVID sub-study Spanish consent form	Consent Form/Addendum	spanish consent form.pdf	Y	No	04/20/2020	Elissa Lynch (el2888)
No	Updated CF tracked changes July 10 2019	Consent Form/Addendum (tracked)	Inulin Consent Form 7.10.19_tracked changes.docx	Y	No	07/11/2019	Dagmara Moscoso (dim2115)
No	CTO IND form signed by D Landry	CTO Form of Notice	CTO IND form signed by D Landry.pdf	Y	No	03/12/2020	Amy Jansen (aj2870)
No	FDA-1571_Abrams_signed	FDA Form/Documentation	FDA-1571_Abrams_signed.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	FDA-1572_completed	FDA Form/Documentation	FDA-1572_completed.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	DoD Award Application Project Narrative	Funding/Grant Application/Subcontract	1-Project Narrative.pdf	Y	No	01/14/2019	Daniel Freedberg (def2004)
No	1-Project Narrative	Funding/Grant Application/Subcontract	1-Project Narrative.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	10-Study Personnel and Organization	Funding/Grant Application/Subcontract	10-Study Personnel and Organization.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	11-Data Management Plan	Funding/Grant Application/Subcontract	11-Data Management Plan.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	12-Transition Plan	Funding/Grant Application/Subcontract	12-Transition Plan.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	13-Regulatory Strategy	Funding/Grant Application/Subcontract	13-Regulatory Strategy.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	14-Representations	Funding/Grant Application/Subcontract	14-Representations.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	2-Supporting Documentation	Funding/Grant Application/Subcontract	2-Supporting Documentation.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	3-Technical and Lay Abstracts	Funding/Grant Application/Subcontract	3-Technical and Lay Abstracts.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	4-Statement of Work	Funding/Grant Application/Subcontract	4-Statement of Work.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	5-Impact Statement	Funding/Grant Application/Subcontract	5-Impact Statement.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	6-Military Relevance	Funding/Grant Application/Subcontract	6-Military Relevance.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	7-Intervention with DSMP	Funding/Grant Application/Subcontract	7-Intervention with DSMP.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	8-Human Subjects and Consent Form	Funding/Grant Application/Subcontract	8-Human Subjects and Consent Form.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	9-Surveys and Questionnaires	Funding/Grant Application/Subcontract	9-Surveys and Questionnaires.pdf	Y	No	03/20/2019	Brenna Posner (bp2538)
No	IND Approval from FDA and Communications	Investigator Brochure/Packaging Insert/Device Manual	IND - all documents.pdf	Y	No	01/14/2019	Daniel Freedberg (def2004)
No	Inulin COVID sub-study protocol with tracked changes	Other	Inulin COVID sub-study tracked changes.pdf	Y	No	03/24/2020	Daniel Freedberg (def2004)
No	verbal phone script for surrogates	Other	Verbal script for phone consent.pdf	Y	No	03/01/2019	Daniel Freedberg (def2004)
No	Department of Defense Report (for annual renewal process)	Other	W81XWH Year 1 Quarter 4 (Annual) Report.pdf	Y	No	03/04/2021	Elissa Lynch (el2888)
No	Pathology approval for residual blood	Pathology Approval Form	Path19-54_AAAS2576_Freedberg.pdf	Y	No	03/01/2019	Daniel Freedberg (def2004)
No	DSMP included in DoD Application	Safety/Monitoring Report	7-Intervention with DSMP.pdf	Y	No	01/14/2019	Daniel Freedberg (def2004)
No	DSMB Report (for annual renewal process)	Safety/Monitoring Report	DSMP Report 1.pdf	Y	No	03/04/2021	Elissa Lynch (el2888)
No	Inulin Trial Protocol v5 February 24, 2020	Standalone/Sponsor's Protocol	Trial Protocol_2.24.20.pdf	Y	No	02/24/2020	Elissa Lynch (el2888)
No	Inulin Trial Protocol v3 April 8, 2019	Standalone/Sponsor's Protocol	Trial Protocol_4.8.19.pdf	Y	No	07/24/2019	Daniel Freedberg (def2004)
No	Trial Protocol_3.25.20_highlighted_changes	Standalone/Sponsor's Protocol (tracked)	Trial Protocol_3.25.20_highlighted_changes.docx	Y	No	03/25/2020	Amy Jansen (aj2870)
No	3 month telephone questionnaire and script	Study Material/Instrument	3 Month Assessment.pdf	Y	No	02/26/2019	Daniel Freedberg (def2004)
No	6 month telephone assessment and script	Study Material/Instrument	6 Month Assessment.pdf	Y	No	02/26/2019	Daniel Freedberg (def2004)
No	Spanish Consent Form	Translated Study Material	Inulin CF Spanish July 19 2019.pdf	Y	No	07/19/2019	Dagmara Moscoso (dim2115)

Tasks

Appendix 9.4

Columbia University Consent Form

Principal Investigator: Daniel E. Freedberg

Attached to Protocol: IRB-AAAS2576

Protocol Title: Inulin for the Prevention of Antibiotic-Resistant Infections in the ICU

Contact Information	Title	Contact Information
Elissa Lynch	Research Nurse	Phone: 212-304-5737 Cell: 412-779-8369 Email: el2888@cumc.columbia.edu
Daniel Freedberg	Principal Investigator	Phone: 212-342-3302 Cell: 857-998-9370 Email: def2004@cumc.columbia.edu

KEY INFORMATION

What is being asked of me?	This form seeks your consent to participate in a research study.
Why is this research being done?	This research tests whether inulin, a fiber supplement made from chicory root, encourages the growth of “good” bacteria to prevent infections in the ICU.
What does it involve?	Two thirds of the patients in this study will receive inulin and one third will receive placebo. All of the patients will have non-invasive assessments where samples and information will be gathered.
How long does it last?	While you are in the hospital, with telephone calls at 3 months and 6 months.
Risks?	Inulin causes bloating in some studies but has no known serious side effects.
Benefits?	Inulin may breed “good” bacteria to help to fight infections but this is not proven.
Alternatives?	There is no obligation to participate. The care you get here will be identical whether you do or do not participate.

Purpose of this form

The purpose of this form is to give you information so that you can decide if you want to take part in the study while in the intensive care unit (ICU). Many ICU patients are not capable of making decisions on their own, and this form is written to address both the patient or the patient’s surrogate decision maker as “you.”

Why am I being asked about this study?

Because you are hospitalized in the ICU, have a known or suspected infection, and are on antibiotic.

Why is this study being done?

Infection is the number one killer in the ICU. This study is being done to test **inulin** as an investigational new drug (not FDA approved) to prevent infections. Patients are “randomized” so that 2 out of 3 patients get the drug but no one knows who will get the drug and who will not.

What happens to me in this study?

If you choose to participate, you will receive either inulin 32 g/day, inulin 16 g/day, or placebo. Two thirds of the patients get inulin and 1/3 of the patients get placebo. No one, including you and the ICU team, will know whether you are getting inulin or placebo.

We will perform a total of 5 assessments: now and again in 3, 7, 14, and 30 days as long as you are hospitalized here. If you are about to be discharged, we will perform an assessment before you leave. No assessments are done once you go home but after 3 and 6 months we will call you to check how you are doing. This call has 13 questions and lasts 5-10 minutes. At each assessment, we look at your medical chart, and take the following samples:

Sample type	What it means for me
Rectal swabs	Two soft nylon swabs will be gently inserted into the anal area to gather bacteria.
Whole stools	A stool that you make will be taken.



Columbia University IRB

IRB-AAAS2576 (Y03M00)

IRB Approval Date: 03/17/2021

For use until: 03/16/2022

Oral swab	Two soft cotton swabs will be brushed against your mouth to gather bacteria.
Urine	A tablespoon of urine will be taken after you urinate or from a catheter, if you have one.
Residual blood samples	About 2 tablespoons of blood will be taken from blood that was already drawn for normal tests. Most of this blood is thrown away, and we will use the “leftover” blood if there is any. You will <i>not</i> have a blood draw as part of this study.

Risks

Inulin comes from dried chicory (a root vegetable). It is a common food additive and is slightly sweet (the placebo in this study is also slightly sweetened to match). A common side effect of inulin is bloating, which goes away on its own. Some studies have reported that inulin worsens diarrhea whereas other studies have reported that inulin improves diarrhea. Inulin has been used in the ICU with other fibers before and appears to be safe, but it is possible that we will discover new effects of inulin which could be good or bad.

With the samples gathered, there is risk of discomfort, emotional embarrassment, and inconvenience. For the rectal swab, we will ask you to turn onto your side and we will ask that your family leave the room for a moment to preserve your privacy.

With both the samples and the health information gathered, there is always a risk of a breach of confidentiality if your data is lost. This is discussed below, and safeguards are in place to make sure that this doesn't happen.

Benefits

Our hope is that inulin encourages the growth of good bacteria and therefore may help to prevent infections. However, this study was not designed to directly benefit subjects. Future ICU patients may benefit from the knowledge that we gain by doing this study.

Alternative procedures

The alternative is not to participate. All of the other care that you receive will be identical regardless of whether or not you take part in the study.

Confidentiality

Any information collected during this study that can identify you by name will be kept confidential. There will be no human genetic sequencing as part of this study. We will do everything we can to keep your data secure, however, complete confidentiality cannot be promised. Despite all our efforts, unanticipated problems such as a stolen computer can occur, although this is unlikely. To make your data more secure, health information and biological samples will all be assigned a code number and separated from your name or other information that could identify you. The file that links you to the code number will be kept on an encrypted, password-protected computer, and only the principal investigator and the study team will have access to this file.

Additionally, the following agencies will be able to look at and copy your research records: Authorities from Columbia University Medical Center and NewYork-Presbyterian Hospital, the Office of Human Research Protections (“OHRP”), an independent research monitor, the FDA, and the Department of Defense (DoD) Office for Human Research Protections (OHRP). Your participation in this research study will be documented in your electronic medical record in Epic and can be viewed by authorized personnel from Columbia University Irving Medical Center, Weill Cornell Medical Center and NYP affiliate institutions who are involved in your health care. A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the study results. You can search this website at any time.

Your authorization to use and share your health information does not have an expiration (ending) date. Once your health information has been disclosed to a third party (for example, a pharmaceutical company participating in a study), federal privacy laws may no longer protect it from further disclosure.

You may change your mind and revoke (take back) this consent and authorization at any time and for any reason. To revoke this consent and authorization, you must contact the Principal Investigator Daniel Freedberg at def2004@cumc.columbia.edu. However, if you revoke your consent and authorization, you will not be allowed to continue taking part in the Research. Also, even if you revoke this consent and authorization, the Researchers and the Sponsor (if applicable) may continue to use and disclose the information they have already collected.

What happens to my samples?

We will retain your samples and data indefinitely. Because our research study is funded by the U.S. Department of Defense (DoD), we are required to submit some data in coded form to one or more databases managed by the Federal government. Some of these databases permit public unrestricted access to the data. The data may be the combined or individual data of many people. Any data that is submitted will not be labeled with your name or other information that could be used to easily identify you. However, it is possible that your information, when combined with information from other public sources, could be used to identify you. We believe that this is unlikely to happen.

If you agree that we may retain and use your samples and/or data indefinitely, they will be stored at CUMC either with the researchers on this study or in a central storage facility called a repository in identifiable form in a coded manner. This means that your samples and/or data will be identified by a unique code number that is linked to your name. The key to the code will be stored securely on an encrypted electronic device.

Also with your permission, your samples and/or data may be used by other Columbia researchers or researchers at other institutions, including commercial companies. If they are given to researchers who are not on this study, they will only be given in de-identified form. This means that your name and other identifying information have been removed from your samples and/or data or that your samples and/or data are coded and the researchers who will use them will not have the key that links your name to the code number.

Any future testing or research using your samples and/or data may lead to the development and use of information, products, tests and/or treatments having commercial value. You will not receive any compensation that may result from these tests or treatments.

Research related injuries

Taking part in this research study may result in injury or harm to you. In the event of an injury resulting from your participation in this study, you should seek appropriate medical care and inform the study doctor. In the event of an emergency you should go to an emergency room. If you are injured or harmed as a result of participating in the study and receive medical care through the NewYork-Presbyterian Hospital (NYPH), a Columbia doctor, or any other health provider, you will be sent a bill for whatever medical care you receive. All or part of your bill may be paid by your health insurance. The study sponsor will not pay for any medical expenses, even if these medical expenses result from participation in the study. Columbia University and NewYork-Presbyterian Hospital (NYPH) are not offering to provide you the drug/device after the termination of the study or to pay you for pain, worry, lost income, the cost of your medical care or non-medical care costs that might occur as a result of your taking part in this study. However, you do not waive any of your legal rights in signing this form.

Compensation

There is no compensation. If your samples result in some commercial profit, you will not share in this profit.

Additional Costs

There are no costs for taking part in this study.

Voluntary Participation

Taking part in this study is your choice. You can decide not to take part in or stop being in the study at any time. Your choice will not affect the treatment you receive from doctors and staff at Columbia University Medical Center and NewYork-Presbyterian Hospital.

Will results be returned to me?

The tests for this study will be performed at the end of the study, long after you have left the ICU. None of these test results are likely to have an impact on your future healthcare, and there are no plans to return any test results to you.

Whom Do I Call if I Have Questions?

If you have any questions about your rights as a subject, you may contact the Principal Investigator of the



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study Dr. Freedberg at 212-342-3302 (research office) or 212-305-1021 (clinical office) if you have any questions or concerns. You may also contact the institutional review board (IRB) at the following location. Human Research Protection Office, Institutional Review Board, Columbia University Medical Center, 154 Haven Avenue, 1st Floor, New York, NY 10032, Telephone: (212) 305-5883, Email: irboffice@columbia.edu.

An IRB is a committee organized to protect the rights and welfare of human subjects involved in research. More information about taking part in a research study can be found on the Columbia University IRB website at: <http://www.cumc.columbia.edu/dept/rb>.

Statement of Consent

I have read this consent form and the research study has been explained to me. I agree to be in the research study described above. A copy of this consent form will be provided to me after I sign it. By signing this consent form, I have not given up any of the legal rights that I would have if I were not a participant in the study.

Participant Signature Lines

Study Participant

Print Name _____ Signature _____
Date _____

Legally Authorized Representative

Print Name _____ Signature _____
Date _____

Research Signature Lines

Principal Investigator

Print Name _____ Signature _____
Date _____

Study Coordinator

Print Name _____ Signature _____
Date _____



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Appendix 9.5

Formulario de Consentimiento de la Universidad de Columbia

Investigador Principal: Daniel E. Freedberg

Adjunto al Protocolo: IRB-AAAS2576

Título del Protocolo: Inulina para la prevención de las infecciones resistentes a los antibióticos en la Unidad de Cuidados Intensivos

Información de Contacto	Título	Información de Contacto
Elissa Lynch	Enfermera de Investigación	Teléfono: 212-304-5737 Móvil: 412-779-8369 Correo electrónico: el2888@cumc.columbia.edu
Daniel Freedberg	Investigador Principal	Teléfono: 212-342-3302 Móvil: 857-998-9370 Correo electrónico: def2004@cumc.columbia.edu

INFORMACIÓN CLAVE

¿Qué me están pidiendo?	Este formulario busca su consentimiento para participar en un estudio de investigación.
¿Por qué se está realizando esta investigación?	Esta investigación comprueba si la inulina, un suplemento de fibras fabricado de la raíz de achicoria, estimula el crecimiento de bacterias “buenas” para prevenir las infecciones en la Unidad de Cuidados Intensivos (ICU por sus siglas en inglés).
¿En qué consiste?	Las dos terceras partes de los pacientes en este estudio recibirán la inulina y una tercera parte recibirá el placebo. Todos los pacientes tendrán evaluaciones no invasivas donde se recogerán muestras e información.
¿Qué tiempo durará el estudio?	Mientras usted permanezca en el hospital, con llamadas telefónicas a los 3 meses y 6 meses.
¿Riesgos?	En algunos estudios se ha observado que la inulina causa distensión abdominal, pero no se conocen efectos secundarios graves.
¿Beneficios?	La inulina puede hacer crecer las bacterias “buenas” para ayudar a luchar contra las infecciones, pero no se ha comprobado.
¿Alternativas?	No hay obligación de participar. La atención que usted recibe aquí será igual si participa o no participa.

Propósito de este formulario

El propósito de este formulario es brindarle a usted la información para que pueda decidir si quiere participar en el estudio mientras está en la Unidad de Cuidados Intensivos (ICU). Muchos pacientes en la Unidad de Cuidados Intensivos (ICU) no pueden tomar sus propias decisiones y este formulario está dirigido tanto para el paciente como para el sustituto del paciente para tomar decisiones como “usted”.

¿Por qué me piden estar en este estudio?

Porque usted está hospitalizado en la Unidad de Cuidados Intensivos (ICU), tiene una infección o se sospecha la presencia de una infección y está recibiendo antibióticos.

¿Por qué se lleva a cabo este estudio?

La infección es la causa de muerte número uno en la Unidad de Cuidados Intensivos (ICU). El estudio se realiza para poner a prueba la **inulina** como un nuevo medicamento bajo investigación (no aprobado por la Administración de Alimentos y Medicamentos, FDA por sus siglas en inglés) para prevenir las infecciones. Los pacientes son asignados de manera “aleatoria” para que 2 de 3 pacientes reciban el medicamento, pero nadie sabe quién recibe el medicamento y quién no lo recibe.



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¿Qué me sucede en este estudio?

Si elige participar, usted recibirá la inulina 32 g/día, inulina 16 g/día o placebo. Las dos terceras partes (2/3) de los pacientes recibirán la inulina y la tercera parte (1/3) de los pacientes recibirá el placebo. Nadie, incluyéndolo a usted y al grupo de la Unidad de Cuidados Intensivos (ICU), sabrá si usted está recibiendo inulina o placebo.

Realizaremos un total de 5 evaluaciones: ahora y otra vez a los 3, 7, 14 y 30 días, siempre y cuando usted esté hospitalizado aquí. Si usted está a punto de ser dado de alta, realizaremos una evaluación antes de irse. No se harán las evaluaciones una vez que se vaya a su casa, pero después de los 3 y 6 meses lo llamaremos para saber cómo está. En esta llamada le haremos 13 preguntas y durará 5-10 minutos. En cada evaluación, revisaremos su expediente médico y obtendremos las siguientes muestras:

Tipo de muestra	Qué significa para mí
Pasar un hisopo rectal	Dos hisopos suaves de nylon se insertarán suavemente dentro del área anal para recoger bacterias.
Heces fecales	Se recogerán las heces que usted haga.
Pasar un hisopo bucal	Dos hisopos suaves de algodón se frotarán en la mejilla para recoger bacterias.
Orina	Se recogerá una cucharada de orina después que usted orine o de un catéter, si tiene uno colocado.
Muestras de sangre residual	Se obtendrán unas 2 cucharadas de la sangre que ya fue extraída para análisis habituales. La mayoría de esta sangre se desecha y nosotros usaremos la sangre que “sobre”, si hay alguna. A usted no se le sacará sangre como parte de este estudio.

Riesgos

La inulina proviene de la achicoria seca (la raíz de un vegetal). Este es un aditivo común de los alimentos y es ligeramente dulce (el placebo en este estudio también está ligeramente endulzado para que se parezcan). Un efecto secundario común de la inulina es la distensión (hinchazón) abdominal, que desaparece sola. Algunos estudios han reportado que la inulina empeora la diarrea, sin embargo, otros estudios han reportado que mejora la diarrea. La inulina se ha usado antes en la Unidad de Cuidados Intensivos (ICU) con otras fibra y parece ser segura (inocua, no hace daño), pero es posible que se descubra algún efecto nuevo de la inulina que pueda ser bueno o malo.

Con las muestras recogidas, existe el riesgo de molestia, sentimientos de vergüenza e inconvenientes. Para colocar el hisopo rectal, le pediremos que se voltee de lado y que su familia salga de la habitación por un momento para preservar su privacidad.

Con las muestras y la información de salud recogidas, existe siempre el riesgo de violación de la privacidad si se pierden sus datos. Esto se discute posteriormente y se han implementado salvaguardas para garantizar que esto no suceda.

Beneficios

Esperamos que la inulina estimule el crecimiento de las bacterias buenas y por lo tanto, pueda ayudar a prevenir las infecciones. Sin embargo, este estudio no fue diseñado para beneficiar directamente a los sujetos. Los pacientes futuros de la Unidad de Cuidados Intensivos (ICU) pueden beneficiarse del conocimiento que hemos obtenido por realizar este estudio.

Procedimientos alternativos

La alternativa es no participar. Todos los otros cuidados que usted recibe serán idénticos, independientemente de si usted participa o no en el estudio.

Confidencialidad

Toda información recopilada durante este estudio que pueda identificarlo por su nombre se mantendrá confidencial. No habrá secuenciación genética humana como parte de este estudio. Haremos todo lo posible para mantener sus datos seguros. Sin embargo, no podemos prometer completa confidencialidad. A pesar de todo nuestro esfuerzo, pueden ocurrir problemas imprevistos, tales como el robo de una computadora, aunque esto es muy poco probable. Para hacer más seguros sus datos, a toda la información de salud y a las muestras biológicas le asignarán un número de código y estarán separadas de su nombre o de cualquier otra información que pueda identificarle. El archivo que lo vincula a usted con el número de código se mantendrá en una computadora codificada y protegida por contraseña y solamente el investigador principal y el personal del estudio tendrán acceso a este archivo.

Además, las agencias siguientes podrán mirar y copiar sus expedientes de la investigación: las autoridades del Centro Médico de la Universidad de Columbia y del Hospital New York Presbyterian, la Oficina para la Protección de Humanos en la Investigación ("OHRP", por sus siglas en inglés), un monitor independiente de investigación, la FDA y el Department of Defense (DoD) Office for Human Research Protections (OHRP). Su participación en este estudio de investigación será documentada en su expediente médico electrónico. Este expediente puede ser visto por el personal autorizado del Centro Médico Irving de la Universidad de Columbia (*Columbia University Irving Medical Center*), Centro Médico Weill Cornell (*Weill Cornell Medical Center*), Hospital New York Presbyterian y sus instituciones afiliadas, porque estas instituciones comparten el sistema de expediente médico electrónico. Los monitores del estudio y otros que supervisan el estudio pueden también necesitar el acceso a este expediente. Una descripción de este estudio clínico estará disponible en <http://www.ClinicalTrials.gov>, como lo exigen las leyes de los Estados Unidos. El sitio web no incluirá información que pueda identificarlo. A lo sumo, el sitio web puede incluir un resumen de los resultados. Usted puede buscar este sitio web en cualquier momento.

Su autorización para usar y compartir su información de salud no tiene fecha de vencimiento. Una vez que su información de salud se haya revelado a una tercera parte (por ejemplo, una compañía farmacéutica que participa en un estudio), las leyes federales de la privacidad posiblemente no la protejan de otras revelaciones. Usted puede cambiar de opinión y revocar (cancelar) este consentimiento y autorización en cualquier momento y por cualquier motivo. Para cancelar este consentimiento y autorización, debe comunicarse con el Investigador Principal, el Dr. Daniel Freedberg en def2004@cumc.columbia.edu. Sin embargo, si usted cancela su consentimiento y autorización, no se le permitirá continuar participando en la investigación. Además, aunque usted cancele este consentimiento y autorización, los investigadores y el patrocinador (si corresponde) pueden continuar usando y revelando la información que ya han recopilado.

¿Qué sucede con mis muestras?

Retendremos sus muestras y datos indefinidamente. Ya que nuestro estudio de investigación está financiado por el Departamento de Defensa (DoD por sus siglas en inglés) de los Estados Unidos, nos exigen presentar algunos datos en forma codificada a una o más bases de datos administradas por el gobierno federal. alguna de estas bases de datos permite el acceso no restringido del público a los datos. Los datos pueden ser datos combinados o individuales de muchas personas. Todo dato que es presentado no será rotulado con su nombre ni otra información pueda ser usada para identificarlo a usted fácilmente. Sin embargo, es posible que su información, cuando se combine con la información de otras fuentes públicas, se pueda usar para identificarlo a usted. Creemos que esto es muy poco probable que ocurra.

Si usted acepta que nosotros podamos retener y usar sus muestras y/o datos indefinidamente, ellos serán almacenados en el Centro Médico de la Universidad de Columbia (CUMC por sus siglas en inglés) o bien con los investigadores en este estudio o en un centro de almacenamiento central, llamado repositorio, de forma identificable de una manera codificada. Esto significa que sus muestras y/o datos serán identificados por un número de código único que es vinculado a su nombre. La clave del código será almacenada de manera segura en un dispositivo electrónico codificado.

También con su permiso, sus muestras y/o sus datos pueden ser usados por otros investigadores de Columbia o investigadores de otras instituciones, incluyendo compañías comerciales. Si son entregados a investigadores que no forman parte de este estudio, se entregarán solamente de forma no identificada. Esto quiere decir que su nombre y otra información de identificación han sido retirados de sus muestras y/o datos o que sus muestras y/o datos están codificados y los investigadores que los usen no tendrán la clave que vincula su nombre al número de código.



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Cualquier prueba o investigación usando sus muestras y/o datos puede dar lugar al desarrollo y uso de información, productos, pruebas y/o tratamientos que tienen valor comercial. Usted no recibirá ninguna compensación que pueda resultar de estas pruebas ni tratamientos.

Lesiones relacionadas con la investigación

Participar en este estudio de investigación puede resultar en lesión o daño a usted. En caso de una lesión que sea resultado de su participación en este estudio, debe buscar atención médica apropiada e informarlo al médico del estudio. En caso de una emergencia debe ir a una sala de emergencia. Si usted se lesiona o se daña como resultado de participar en este estudio y recibe cuidado médico a través del Hospital New York Presbyterian (NYPH por sus siglas en inglés), un médico de Columbia o cualquier otro proveedor de salud, se le enviará una factura por cualquier cuidado médico que reciba. Su seguro de salud puede pagar toda o parte de la factura. El patrocinador del estudio no pagará ningún gasto médico, aun cuando estos gastos médicos sean resultado de su participación en el estudio. La Universidad Columbia y el Hospital New York Presbyterian (NYPH) no están ofreciendo proporcionarle a usted el medicamento/dispositivo después de terminar el estudio ni pagar por su dolor, preocupación, pérdida de ingresos, costo de su cuidado médico ni costos no médicos en los que usted pudiera incurrir a consecuencia de su participación en este estudio. Sin embargo, usted no renuncia a ninguno de sus derechos legales al firmar este formulario.

Compensación

No hay compensación. Si sus muestras dan lugar a algún beneficio comercial, no se compartirá con usted este beneficio.

Costos adicionales

No hay costos por participar en este estudio.

Participación voluntaria

La participación en este estudio es su elección. Puede decidir no participar o dejar de participar en el estudio en cualquier momento. Su elección no afectará el tratamiento que recibe de los médicos ni del personal en el Centro Médico de la Universidad de Columbia y en el Hospital New York Presbyterian.

¿Me entregarán los resultados?

Las pruebas para este estudio se realizarán al final del estudio, mucho después de que usted haya salido de la Unidad de Cuidados Intensivos (ICU). Es posible que ninguno de los resultados de estas pruebas tenga un impacto en su cuidado de salud en el futuro y no hay planes de entregarle ningún resultado de las pruebas.

¿A quién puedo llamar si tengo preguntas?

Si tiene preguntas sobre sus derechos como un sujeto, puede contactar con el Investigador Principal del estudio, el Dr. Freedberg al 212-342-3302 (oficina de investigación) o al 212-305-1021 (consultorio de la clínica) si tiene alguna pregunta o preocupación. También puede contactar con la Comisión Institucional de Revisión (IRB por sus siglas en inglés) en el siguiente lugar: Human Research Protection Office, Institutional Review Board, Columbia University Medical Center, a [154 Haven Avenue, 1st Floor, New York, NY 10032](#), [teléfono: \(212\) 305-5883](tel:(212)305-5883), [correo electrónico: irboffice@columbia.edu](mailto:irboffice@columbia.edu).

Una IRB es un comité organizado para proteger los derechos y el bienestar de los sujetos humanos que participan en investigación. Más información sobre la participación en un estudio de investigación puede encontrarla en el sitio web de la IRB de la Universidad de Columbia en: <http://www.cumc.columbia.edu/dept/rb>.



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Declaración de Consentimiento

He leído este formulario de consentimiento y me han explicado el estudio de investigación. Acepto participar en el estudio de investigación descrito anteriormente. Me proporcionarán una copia de este formulario de consentimiento después de firmarlo. Al firmar este formulario de consentimiento, no renuncio a ninguno de los derechos legales que tendría si no fuera un participante en el estudio.

Líneas de firmas del participante

Participante del estudio

Nombre en letras de imprenta _____ Firma _____

Fecha _____

Representante legalmente autorizado

Nombre en letras de imprenta _____ Firma _____

Fecha _____

Líneas de firmas del miembro de la investigación

Investigador Principal

Nombre en letras de imprenta _____ Firma _____

Fecha _____

Coordinadora del Estudio

Nombre en letras de imprenta _____ Firma _____

Fecha _____



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Appendix 9.6

Inulin in the ICU e-consent form

Please read thoroughly and sign the consent form below if participating.

Thank you!

Study ID

(entered by research staff)

Date/Time

Study Participant's First Name

(el nombre de participante del estudio)

Study Participant's Last Name

(el apellido de participante del estudio)

Consent form (English)

[Attachment: "Inulin Consent Form English.pdf"]

Consent form (Spanish)

[Attachment: "Inulin Consent Form Spanish.pdf"]

HIPAA form (English)

[Attachment: "HIPAA English.pdf"]

HIPAA form (Spanish)

[Attachment: "HIPAA Spanish.pdf"]

Are you a legally authorized representative?

☐ Yes

☐ No

First Name

(Please enter your first name)

Last Name

(Please enter your last name)

Email address

(Please enter your email address to receive a copy of this consent.)

Signature

(Please sign your name with your finger or mouse.)

Appendix 9.7

B2. SOFA SCORE WORKSHEET

Study ID: 4 digits followed by a letter

(4 digit number followed by A, or B if a new subject must be substituted because original subject with this number did not complete Day 3 visit, or C if another substitution must be made. Numbers are assigned consecutively as subjects are randomized, beginning with 1001, 1002 etc. Only randomized subjects are given a Study ID.)

Baseline SOFA will be calculated for patients who have ANY data within the CUMC EMR during the previous 12 months that allows us to calculate a baseline. For most patients, this will be the discharge information from a previous hospitalization, or the information from an outpatient medical visit. The timepoint pertaining to this visit/hospitalization will then be selected and the baseline SOFA will be assessed using the 24 hour period preceding that timepoint. If data is missing, it will be assumed to be normal. The WORST data point over the 24 hour period should always be selected, excluding spurious values.

SOFA Assessment Date

SOFA Assessment Time

Oxygen Flow-Related Data (used to calculate FiO2 delivered, below, for SOFA scoring)

1. Select type of oxygen.

- ☐ 1. room air
☐ 2. nasal canula
☐ 3. nonrebreather (NRB) mask
☐ 4. ventilator including CPAP

1b. Nonrebreather (NRB) mask, Select flow rate

_____ (15-Jan)

1a. Nasal canula, Select flow rate

_____ (15-Jan)

1c. Ventilator including CPAP, Select flow rate

_____ (Enter a number between 20 and 100 in 5 unit increments (e.g. 20, 25, 30....))

2. PaO2 from arterial blood gas .

_____ (Take this value from the arterial blood gas (ABG) measurement with or without lactate. Enter 20-100; if no ABG was not performed during the preceding 24 hours, enter -1)

FiO2 delivered (calculated from above)

3. Platelets -Choose lowest value in 24 hours .

4. Bilirubin in mg/dL - Choose highest value in 24 hours.

5. Glasgow Coma Scale (GCS): This is the assumed GCS in sedated patients. That is, what score would the patient have if he or she was NOT sedated? Within each category, choose the LOWEST value.

5a. GCS Motor - Best motor response.

- ☐ 1 no response
☐ 2 extension to pain
☐ 3 flexion to pain
☐ 4 withdrawal from pain
☐ 5 localizes to pain
☐ 6 obeys commands
 (Most patients will score 1, 5, or 6.)

5b. GCS Verbal - Best verbal response

- ☐ 1 no response
☐ 2 incomprehensible
☐ 3 inappropriate
☐ 4 confused
☐ 5 oriented
 (Intubated patients will score a 1 (no response).)

5c. GCS Eye Response -Best eye response

- ☐ 1 not opening
☐ 2 to pain
☐ 3 to verbal commands
☐ 4 spontaneously

6. Mean arterial pressure (MAP)

(0 - 150. If missing, enter -1 and provide systolic/diastolic blood pressure below)

6a. Systolic blood pressure.

(Enter 1-250)

6b. Diastolic blood pressure

(Enter 1-200)

7. Use of Vasopressors (if yes, provide values below: higher values are worse; single bolus doses should be ignored; all values should be entered with 1 decimal value, e.g, 2.5, 50.6; if a value is not recorded/not available, enter the negative value -1.0).

☐ No ☐ Yes

7a. Dopamine in mcg/kg/min

(.1 to 100.0; enter -1.0 if not recorded)

C Intervention Assignment

This form should be filled out only for subjects who have met all eligibility criteria (Form B1) and who have consented to participate in the study.

1. SCREENING ID (from SCREENING database)

(Example: SCN001, SCN002 etc)

2. Go to the research pharmacy to facilitate administration of the intervention.

☐ Done

3. Enter a clinical note documenting that the patient is participating in a research study.

☐ Done
(This note should include the study IRB number, the time of enrollment, and who gave consent (patient vs surrogate).)

E1. ICU ADMISSION ASSESSMENT

First set of ICU vital signs :

Date

((mm/dd/yyyy))

Time (military)

((military))

Baseline assessment

1. Which sex category best describes the patient?

☐ Male ☐ Female

2. Age in years at the time of ICU admission.

3. Which ethnicity best describes you?

☐ Hispanic
☐ Non-Hispanic

4. Which race best describes you?

☐ White
☐ Hispanic
☐ Black or African American
☐ Asian
☐ Native Hawaiian or Pacific Islander
☐ American Indian or Alaska Native
☐ None of the above

5. Before being hospitalized in the ICU, where were you most recently?

☐ Came from home via the ER
☐ Came from home via the OR (rare)
☐ Hospital floor
☐ Another hospital's ICU
((Surrogate to answer if subject unable.))

6. Which best describes your home environment?

☐ Home, totally independent
☐ Home, with some help
☐ Assisted living facility
((Surrogate to answer if subject unable.))

EMR data, taken from the ICU admission notes

7. Baseline chronic medical comorbidities: CHECK ALL THAT APPLY.

All baseline medical comorbidities should be indicated here, based on the comorbidities listed in the most recent relevant electronic notes. These comorbidities represent the patient's baseline problems (i.e., chronic conditions) and not why he or she was sent to the ICU. Use standardized language.

- ☐ MI/heart attack
- ☐ Congestive heart failure
- ☐ Peripheral vascular disease
- ☐ CVA/stroke or TIA
- ☐ Dementia
- ☐ COPD
- ☐ Peptic ulcer disease
- ☐ Mild liver disease
- ☐ Moderate liver disease (cirrhosis or portal 11,hypertension)
- ☐ Severe liver disease (cirrhosis or portal 13,hypertension and variceal bleeding)
- ☐ Diabetes uncomplicated
- ☐ Diabetes severe - with end organ damage such as retinopathy, neuropathy, nephropathy
- ☐ Hemiplegia
- ☐ Moderate CKD - creatinine > 3 chronically
- ☐ Severe CKD - on dialysis, s/p renal transplant, or with uremia
- ☐ Solid malignant tumor - localized
- ☐ Solid malignant tumor - metastatic
- ☐ Leukemia
- ☐ Lymphoma
- ☐ AIDS - controlled HIV does NOT count
- ☐ Other

Other--List other comorbidities, if any.

8. Primary reason for admission (CHECK ONE)

- ☐ Cardiac arrest
- ☐ GI bleeding
- ☐ Heart failure
- ☐ Liver failure
- ☐ Neurologic including stroke
- ☐ Renal failure
- ☐ Respiratory failure including ECMO
- ☐ Sepsis
- ☐ Toxic ingestion
- ☐ Other

If 'Other' primary reason reason for admission, explain in no more than 2 words, taken based on the admission notes.

E2. ICU FOLLOW-UP ASSESSMENT

Assessment Date _____

If this form could not be completed at this study assessment, please indicate why, skip the remainder of the questions and submit the form; then complete Form H: Patient Disposition Record

- ☐ Death
☐ Discharge
☐ Refusal

1. Presence of lines or catheters.

Done by visual inspection at the bedside at the time of assessment.

Urinary catheter (foley) ☐ Yes ☐ No

Femoral central venous line. ☐ Yes ☐ No

Neck central venous line. ☐ Yes ☐ No

Arterial line. ☐ Yes ☐ No

2. Specific AEs of interest

For all of these, ask the subject first, then ask the nurse if he cannot answer.

2A. During the last 24 hours, has there been bloating or abdominal distension ?

- ☐ none
☐ a little
☐ a moderate amount
☐ a lot or severe

2B. During the last 24 hours, how many stools have been produced _____

2C. During the last 24 hours, what has been the loosest stool consistency ?

- ☐ like water,
☐ like porridge,
☐ loose with chunks,
☐ formed but soft,
☐ formed and hard

EMR data

For each assessment ,this data should be taken for the 24 hour period preceding the relevant assessment. E.g., if the Day 3 assessment was performed at 13:00 on April 23, this data would represent the 24 hour time period from 13:00 April 22 to 13:00 April 23.

1. Arterial pH from arterial blood gas.
If none performed, leave blank and check the indicator below

(6.60 - 8.00 (2 decimals). From the arterial blood gas (ABG) measurement with or without lactate. Take the LOWEST value.)

1a. Indicate if no Arterial pH from arterial blood gas within past 24 hours.

- ☐ No pH from ABG within 24 hours.

2. Lactate from the arterial blood gas or direct lactate measurement--take the LOWEST value.

(two decimal places)

2a. No available lactate from the arterial blood gas or direct lactate measurement with 24 hours .

☐ No lactate from ABG within 24 hours

3. ECMO within the last 24 hours?

☐ Yes ☐ No

4. CVVH within the last 24 hours?

☐ Yes ☐ No

5. Albumin - Choose the LOWEST value in 24 hours.

6. Hematocrit - Choose the LOWEST value in 24 hours.

7. White blood cell count - Choose the HIGHEST value in 24 hours.

(.1 to 100 with one decimal)

8. Electrolytes - For each of the following, enter both the LOWEST and the HIGHEST values during the preceding 24 hours

Glucose from BMP in mg/dL - LOWEST

(integer 10 to 1000)

Glucose from BMP in mg/dL -HIGHEST

(integer 10- - 1000)

Calcium from BMP in mg/dL - LOWEST

(number 5 to 15 with one decimal)

Calcium from BMP in mg/dL - HIGHEST

(5 to 15 with one decimal)

Magnesium in mg/dL - LOWEST

(0 to 10 with one decimal)

Magnesium in mg/dL - HIGHEST

(0 to 10 with one decimal)

Phosphorus in mg/dL - LOWEST

(number 1 to 10 with one decimal)

Phosphorous in mg/dL - HIGHEST

(1 to 10 with 1 decimal)

Potassium from BMP in mmol/L - LOWEST

(number 1 to 10 with one decimal)

Potassium from BMP in mmol/L - HIGHEST

(1 to 10 with 1 decimal)

Sodium from BMP in mmol/L - LOWEST

(integer 50-200)

Sodium from BMP in mmol/L - HIGHEST

(Integer 50 -200)

11. VENOUS lactate during the preceding 24 hours

(0.00 TO 20.00)

EMR data representing ICU interventions

Taken for the 24 hour period preceding the first set of ICU vitals or for the relevant study period if this is a follow-up assessment. E.g., if this was the Day 3 assessment this data would represent the interventions from baseline to Day 3. If this was the Day 7 assessment, it would represent the interventions from Day 3 to Day 7.

1. Receipt of a proton pump inhibitor

☐ Yes ☐ No
(PPIs are esomeprazole, omeprazole, pantoprazole, rabeprazole, lansoprazole, dexlansoprazole. Medications received should be determined based on the doses given in the nursing flowsheets not based on orders.)

2. Receipt of opioids.

☐ yes ☐ No
(Common opioids are fentanyl, morphine, dilaudid, Percocet/oxycodone. Medications received should be determined based on the doses given in the nursing flowsheets not based on orders.)

6. Receipt of antibiotics.

	Yes	No
Aminoglycosides (gentamicin)	☐	☐
B-lactams (e.g., amoxicillin)	☐	☐
Cephalosporins (cefazolin or ceftriaxone)	☐	☐
Daptomycin	☐	☐
Extended-spectrum B-lactams (piperacillin-tazobactam/zosyn)	☐	☐
Fluoroquinolones (levofloxacin)	☐	☐
Lincosamides (clindamycin)	☐	☐
Linezolid	☐	☐
Macrolides (azithromycin)	☐	☐
Metronidazole	☐	☐
Monobactams (meropenem, ertapenem)	☐	☐
Polymixin	☐	☐
Sulfonamides (Bactrim)	☐	☐
Tetracyclines (doxycycline)	☐	☐
Vancomycin	☐	☐

G1. SAMPLE COLLECTION: RECTAL SWAB, ORAL SWAB, AND URINE

Form Completed

☐ Yes ☐ No

Reason

☐ death ☐ discharge
☐ refusal
(Fill out Form H--Disposition)

RECTAL SWABS- Two pre-moistened flocked Copan diagnostics swabs; one is flash frozen at -80C and the other is brought on soy broth with 20% glycerol to the ACU lab.

ORAL SWABS- Two EpiCentre cotton-tipped swabs, flash frozen.

URINE SAMPLES- 2 X 8MI urine aliquots, flash frozen

Sample Date (mm/dd/yyyy)

Sample Time (military)

Rectal

☐ Yes/collected ☐ No/not collected

Oral

☐ Yes/collected ☐ No/not collected

Urine

☐ Yes/collected ☐ No/not collected

G2. SAMPLE COLLECTION: WHOLE STOOLS

Work with the nurses to collect 4 X 8mL aliquots of whole stool from each period. The times recorded should represent the date/time WHEN THE STOOL WAS PRODUCED as best as we can tell. For stools, stool 1 refers to the stool produced from after the intervention has been received until Day 3, stool 2 from Day 3 until Day 7, etc. Record the stool collection information at the end of the appropriate time period, e.g. record baseline to Day 3 stool collection at Day 3 in REDCap, etc.

Form Completed

☐ Yes ☐ No

Reason

☐ death ☐ discharge
☐ refusal
(Complete form H: Disposition)

Stool Collection Date

Stool Collection Time

((military))

G3. RESIDUAL BLOOD SAMPLES

Residual Blood Form Completed

☐ Yes ☐ No

Reason

☐ death ☐ discharge
☐ refusal
(FILL OUT FORM H: DISPOSITION)

Residual Blood Date

Residual Blood Time

((military))

K. POST-DISCHARGE ASSESSMENT

Post-Discharge Assessment Completed	☐ Yes ☐ No
Reason	☐ death ☐ discharge ☐ refusal (Fill out Disposition--Form H)
Post-Discharge Assessment Date	_____
Post-Discharge Assessment Time	_____
Who is answering the questions?	☐ Subject ☐ Surrogate ☐ Caregiver ☐ Relative
Is the patient living?	☐ Yes ☐ No
If no, confirm that date of death has been entered and the remaining forms can be closed	_____
In what kind of a place is the patient living?	☐ Home, totally independent ☐ Home, with some help ☐ Assisted living facility
On a scale from 0 to 100 where 0 is the worst health imaginable and 100 is the best, how would you describe your health TODAY?	_____
Has the patient been hospitalized since discharge from the index admission at CUMC?	☐ Yes ☐ No
If yes, enter the best approximation of the date of the start of the first hospitalization following discharge.	_____

Katz Index of Independence

Bathing

- ☐ Bathes self completely or needs help bathing only a single part of the body such as the back
☐ Needs help with bathing more than one part of the body

Dressing

- ☐ Gets clothes from closets and drawers and puts them on, may have help tying shoes
☐ Needs help with dressing

Toileting

- ☐ Goes to the toilet, gets on and off, and arranges clothes
☐ Needs help transferring to the toilet, cleaning, or using bedpan

Transferring

- ☐ Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.
- ☐ Needs help in moving from bed to chair or in completing transfer

Continence

- ☐ Exercises complete self control over urination and defecation
- ☐ Is partially or wholly incontinent of bowel or bladder

Feeding

- ☐ Gets food from plate into mouth without help. Food prep may be done by another person.
- ☐ Needs partial or total help with feeding or requires parenteral feeding

L. POST-DISCHARGE HEALTH QUESTIONNAIRE

Post Discharge Health Form Date

Post Discharge Health Form Time

Mobility

- ☐ I have no problems in walking about
- ☐ I have slight problems in walking about
- ☐ I have moderate problems in walking about
- ☐ I have severe problems in walking about
- ☐ I am unable to walk about

Self-Care

- ☐ I have no problems washing or dressing myself
- ☐ I have slight problems washing or dressing myself
- ☐ I have moderate problems washing or dressing myself
- ☐ I have severe problems washing or dressing myself
- ☐ I am unable to wash or dress myself

Usual Activities (ex: work, study, housework, family, or leisure activities)

- ☐ I have no problems doing my usual activities
- ☐ I have slight problems doing my usual activities
- ☐ I have moderate problems doing my usual activities
- ☐ I have severe problems doing my usual activities
- ☐ I am unable to do my usual activities

Pain/Discomfort

- ☐ I have no pain or discomfort
- ☐ I have slight pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have severe pain or discomfort
- ☐ I have extreme pain or discomfort

Anxiety/Depression

- ☐ I am not anxious or depressed
- ☐ I am slightly anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am severely anxious or depressed
- ☐ I am extremely anxious or depressed

F. INTERVENTION ADMINISTRATION RECORD

Date

Time

((military))

Dose

Date (mm/dd/yyyy)

Time (military) from start of dose

Check if complete dose administered

☐ complete ☐ incomplete

if incomplete, how many mL was administered

J. CULTURE-PROVEN INFECTIONS

Infection Date

Suspected Site

- ☐ Blood
- ☐ Urine
- ☐ Respiratory
- ☐ Wound or soft tissue
- ☐ Stool
- ☐ Other

Suspected Site

Organism

- ☐ Escherichia coli
- ☐ Clostridium difficile
- ☐ MRSA
- ☐ MSSA
- ☐ Klebsiella pneumonia
- ☐ Psuedomonas aeruginosa
- ☐ Serratia marcescens
- ☐ Stenotrophomonas
- ☐ VRE
- ☐ Other

If 'Other', please specify organism

Antibiotic Resistance

- ☐ Amikacin
- ☐ Ampicillin-Sulbactam
- ☐ Aztreonam
- ☐ Cefazolin
- ☐ Cefepime
- ☐ Cefoxitin
- ☐ Cetazadime
- ☐ Ceftriaxone
- ☐ Ertapenem
- ☐ Gentamycin
- ☐ Levofloxacin
- ☐ Meropenem
- ☐ Nitrofurantoin
- ☐ Piperacillin-Tazobactam
- ☐ Tetracycline
- ☐ Tobramycin
- ☐ Bactrim
- ☐ Tigecycline

Comments

I. AE-UP RECORD

Date of UP Onset

Description of unanticipated problem

(100 characters or less)

Date of UP End

UP Severity

- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Life threatening

UP Relatedness to study intervention

- ☐ Possibly
- ☐ Likely related
- ☐ Definitely related

Action on UP

- ☐ None
- ☐ Intervention altered
- ☐ Intervention discontinued
- ☐ Medical intervention
- ☐ Surgical intervention

H. PATIENT DISPOSITION RECORD

Completed	☐ Yes ☐ No
Reason	☐ death ☐ discharge ☐ refusal
Date	
Time	
ICU discharge date	
Hospital discharge date	
Withdrawal date (if withdrew)	
Did the patient die before study completion?	☐ No ☐ Yes
Death date	
Enter a proximate cause of death in 1-2 words	
Last study evaluation date This represents the date on which the final set of samples were taken.	

Appendix 9.8

Daniel E. Freedberg, M.D., M.S.
Division of Digestive and Liver Diseases
Columbia University Medical Center
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Positions

July 2020 – present	Herbert Irving Assistant Professor of Medicine and Epidemiology, Columbia University Medical Center
July 2018 – June 2020	Assistant Professor of Epidemiology, Mailman School of Public Health, Columbia University Medical Center
July 2015 – June 2020	Assistant Professor of Medicine, Division of Digestive and Liver Diseases, Columbia University Medical Center
July 2014 – June 2015	Instructor of Medicine, Division of Digestive and Liver Diseases, Columbia University Medical Center

Training

July 2011 – June 2014	Fellow in Gastroenterology and Hepatology, Division of Digestive and Liver Diseases, Columbia University Medical Center
July 2009 – June 2011	Resident in Medicine, Columbia University Medical Center
July 2008 – June 2009	Intern, Columbia University Medical Center

Education

July 2012 – May 2014	M.S., Patient-Oriented Research, Mailman School of Public Health, Columbia University
Sept 2004 – June 2008	M.D., Harvard Medical School
Sept 2001 – May 2003	Certificate in pre-medical studies, Columbia University
Sept 1993 – June 1997	B.A., History major, Northwestern University

Licensure

New York State License, Internal Medicine (exp. Sept 2016)
Board certified in Internal Medicine, American Board of Internal Medicine, 2011 (exp. 2021)
Board certified in Gastroenterology, 2014 (exp. 2024)

Previous work experience

Simon & Schuster, New York, Aug. 1998 – Sept. 2001
Acquired, edited, and published general interest, serious nonfiction books, specializing in history. Editorial Assistant (until Aug. 1999), Assistant Editor (until June 2000), and Associate Editor (until Sept. 2001).

Awards & honors

2019	Selected as an AGA Future Leader
2018	Selected for Irving Institute “Reach for the R01” competitive grant workshop
2017	Ewig Clinical Scholar Award for outstanding teaching for medical students, house staff, and fellows (\$15,000 annually for three years)
2017	John N. Loeb annual lecture on hospital-associated <i>C. difficile</i> infection
2017	EPIC scholarship award, National Institute for General Medical Sciences
2016	One of top ten most influential articles of the year, IDweek 2016 (for the article on risk for <i>C. difficile</i> related to the prior bed occupant, <i>JAMA Int Med</i> 2016)
2016	Selected for AGA Institute-AASLD Annual Academic Skills Workshop

2012	Arnold P. Gold Foundation Humanism and Excellence in Teaching Award
2011	Best Graduating Resident in Medicine, Columbia-Presbyterian Hospital
1997	History Department Thesis Honors, Northwestern University

Professional organizations and service

2020 – 2021	American Gastroenterological Association (AGA), Nominating Committee This committee provides overall direction for the AGA and selects the AGA governing board (AGA president, etc.). I was chosen as the early career research member.
2020 – 2022	American Gastroenterological Association (AGA), Microbiome and Microbial Therapy (MMT) Nominating Committee This committee helps the AGA to organize content related to the microbiome and to select the next MMT chair.
2019 – present	Scientific Advisory Council, Peggy Lillis Foundation This charitable foundation is dedicated to publication and advocacy related to <i>Clostridioides difficile</i> infection.
2016 – 2019	Executive Committee, Society of Practitioners of Columbia-University Medical Center This voluntary society meets weekly with the hospital administration. The society provides a mechanism that allows doctors to help determine what exemplary patient care means at Columbia.

Society memberships

2011 – present	American Gastroenterological Association
2011 – present	American College of Gastroenterology
2011 – present	American Society of Gastrointestinal Endoscopy
2011 – present	New York Society for Gastrointestinal Endoscopy
2008 – present	American Medical Association
2004 – present	Massachusetts Medical Society

Editorial activities

Associate editor	ACG Case Reports Journal (2013-2014), one of eight founding associate editors
Editorial board	World Journal of Gastroenterology (2013-2016)
Manuscript review (<i>selected</i>)	American Journal of Infection Control Annals of Internal Medicine (highest quality reviewer) Annals of the New York Academy of Sciences BMC Gastroenterology British Medical Journal, Gastroenterology Cancer Prevention Research Clinical Gastroenterology and Hepatology Digestive Diseases and Sciences Expert Opinion on Drug Safety Gastroenterology Gut JAMA Internal Medicine Journal of Gastroenterology and Hepatology PLoS One Practical Gastroenterology

Scientific Reports
Therapeutic Advances in Endoscopy

Grant Review

2019	Study Section, Department of Defense PRMRP (Peer-Reviewed Medical Research Program)
2019	Study Section, NIH CRFS (Clinical Research and Field Studies of Infectious Diseases)
2018	Irving Institute (Columbia CTSA) KL2 Reviewer

Clinical work

Attending Physician, Division of Digestive Diseases, Columbia University (since July 2014)

- Active general gastroenterology clinical practice with 1 office session and 1 endoscopy sessions per week generating 2,000-2,500 work RVUs/year since FY14
- 1-2 weeks attending on General GI (consult) service annually
- 1 mos attending on General Medicine 2 (primary) service every other year

Ongoing Research Support

Columbia-NYU-Takeda Alliance Award (Wang, PI) Jan 2021 – Dec 2021
Project title: Systematic discovery of bile acid metabolizing gut microbiota for IBD treatment
Goal: To conduct high-throughput discovery and cultivation of novel gut microbiota associated with generation of secondary bile acids through computational analysis of gut microbiota genomes and experimental isolation of target species.
Role: Co-I

Irving Scholars Award, Columbia Irving Institute for Clinical and Translational Research (Freedberg, PI) July 2020 – June 2023
Project title: Leveraging gut colonization resistance to prevent multidrug resistant infections in the intensive care unit
Goal: The purpose of this intensive care unit-based translational research is to (1) identify 1:1 bacterial interactions that prevent gut colonization with multidrug-resistant organisms, (2) risk-stratify patients by testing whether the novel microbiome-based biomarker urine 3-indoxyl sulfate predicts loss of colonization resistance, and (3) elucidate how colonization with multidrug-resistant organisms leads to infection by determining the relationship between gut colonization and systemic infection at the strain level.
Role: PI

Digestive Diseases Research Center Pilot (Freedberg, PI) Jan 2020 – Dec 2020
Project title: Preventing multidrug-resistant organism enteric colonization in the intensive care unit
Goal: This project award will use previously collected fecal samples from ICU patients to understand the bacteria-bacteria interactions that prevent or facilitate gut colonization with multidrug-resistant organisms and how this process is shaped by antibiotics.
Role: PI.

Clinical Trial Award (Freedberg, PI) July 2019 – June 2023
Department of Defense (DoD) Peer-Reviewed Medical Research Program (PRMRP)
Project title: Prebiotic inulin to limit antimicrobial-resistant infections during critical illness: a phase II clinical trial
Goal: The purpose of this research is to perform a double-blind, randomized trial of inulin supplementation for the purpose of preventing multidrug-resistant organism colonization and infection in critically ill patients meeting sepsis criteria.

Role: PI.

NIH K23 DK111847 (Freedberg, PI) Feb 2017 – Dec 2020
Project title: Loss of Gastrointestinal Colonization Resistance and Antibiotic-Resistant Infections in the Intensive Care Unit.
Goal: This 4 year mentored research award has enabled me to expand our ICU cohort to study dynamic changes within the gastrointestinal microbiome, with a new focus on antibiotic resistance.
Primary mentor: Timothy Wang.
Role: Mentored PI.

Completed Research Support

Irving Institute/CTO Pilot (Freedberg, PI) July 2018 – June 2019
Project title: Dietary fiber to prevent loss of gastrointestinal colonization resistance and pathogen colonization in the intensive care unit.
Goal: This pilot award offered through Columbia's CTSA (NCATS UL1 TR001873) funds enrollment for a prospective clinical trial comparing high- versus low-fiber feeds in the ICU.
Role: PI.

Feldstein Medical Foundation (Freedberg, PI) July 2018 – June 2019
Project title: Dietary fiber to prevent pathogen colonization in the intensive care unit.
Goal: This medical foundation pilot award funds additional analyses for the ongoing ICU-based fiber study.
Role: PI.

Research Scholar Award (Freedberg, PI) July 2015 – June 2018
American Gastroenterological Association (AGA)
Project title: Clinical and gut microbiome factors associated with ICU-acquired infections.
Goal: This 3 year mentored research award allowed me to build an ICU cohort with collection of biospecimens and data for the purpose of studying ICU-acquired infections.
Primary mentor: Timothy Wang.
Role: Mentored PI.

NIH KL2 TR000081 (Ginsberg, PI) July 2014 – June 2016
Clinical and Translational Sciences Award
Project title: Adverse effects of proton pump inhibitors on the gastrointestinal health of children.
Goal: This 2 year mentored research award included didactic training and enabled me to build a cohort of children who were studied to assess the effects of acid suppression medications on gut health.
Primary mentor: Timothy Wang.
Role: Mentored awardee.

Clinical Research Award (Abrams, PI) July 2014 – Dec 2015
American College of Gastroenterology (ACG)
Project title: Proton pump inhibitors and *Clostridium difficile* infection in children.
Goal: This project specific award enabled us to build a large retrospective cohort related to CDI.
Role: Co-Investigator

NIH UL1 RR024156 (Ginsberg, PI) July 2012 – June 2014
Fundamentals of Patient-Oriented Clinical Research

Goal: This training grant from the Mailman School of Public Health facilitates biostatistical and epidemiological training in clinical research and enabled me to obtain a Master's degree in biostatistics and other additional training during GI fellowship.

Role: Training award recipient.

NIH T32 DK083256-04 (Wang, PI)

July 2012 – June 2014

Multidisciplinary Training in Translational Gastrointestinal and Liver Research

Goal: This training grant facilitates the career development of basic, clinical, and translational researchers and funds from this grant were combined with NIH UL1 RR024156 to enable me to obtain post-graduate training in epidemiology and biostatistics at the Mailman School.

Role: Training award recipient.

Student/training grants

National Kidney Foundation Resident-Investigator Grant, Fall 2008

American Federation of Aging Research Geriatric Scholars Program, Summer 2005

PASTEUR Fellowship (Patient-Associated Science: Training, Education, Understanding, and Research), Harvard Medical School, Summer 2005

Louis E. Kirstein Fellowship, Harvard Medical School, 2004 – 2006

Publications

Original, peer-reviewed research

1. Kuo SZ, Dettmer K, Annavajhala MK, Chong DH, Uhlemann AC, Abrams JA, Oefner PJ, **Freedberg DE**. Associations between urinary 3-indoxyl sulfate, a gut microbiome-derived biomarker, and patient outcomes after intensive care unit admission. *Journal of Critical Care*, *Accepted for publication Jan 19, 2021*.
2. Laszkowska M, Kim J, Faye AS, Joelson AM, Ingram M, Truong H, Silver ER, May B, Greendyke WG, Zucker J, Lebwohl B, Hur C, **Freedberg DE**. Prevalence of *Clostridioides difficile* and other Gastrointestinal Pathogens in Patients with COVID-19. *Digestive Diseases and Sciences*, *Accepted for publication December 3, 2020*.
3. Axenfeld E, Greendyke WG, Li J, Green DA, Whitter S, **Freedberg DE**. Burden and risk factors for inappropriate *Clostridioides difficile* infection testing among hospitalized patients. *Diagnostic Microbiology & Infectious Disease*, *Accepted for publication November 30, 2020*.
4. Zhou MJ, Kamal A, **Freedberg DE**, Markowitz D, Clarke JO, Jodorkovsky D. Type II achalasia is increasing in prevalence. *Digestive Diseases and Sciences* 2020, *Accepted for publication October 7, 2020*.
5. Laszkowska M, Faye AS, Kim J, Truong H, Silver ER, Ingram M, May B, Ascherman B, Bartram L, Zucker J, Sobieszczyk ME, Abrams JA, Lebwohl B, **Freedberg DE**,* Hur C. Disease Course and Outcomes of COVID-19 Among Hospitalized Patients with Gastrointestinal Manifestations. *Clinical Gastroenterology and Hepatology*, *Accepted for publication September 26, 2020*. *Co-senior author with Chin Hur.
6. Jang S, Lebwohl B, Abrams JA, Green PHR, **Freedberg DE**, Alaedini A. Celiac disease serology and gut microbiome following proton pump inhibitor treatment. *Medicine (Baltimore)* 2020 Aug 28; 99(35): e21488. PMID: 32871870 PMCID: PMC7458245
7. Blackett JW...**Freedberg DE**, Mahadev S. Characteristics and outcomes of patients undergoing endoscopy during the COVID-19 pandemic: a multicenter study from New York City. *Digestive Diseases and Sciences* 2020 Sep 15. PMID: 32930898
8. Zachariah P, Rozenberg FD, Stump S, Moscoso D, Krishnamurthy G, Saiman L, Uhlemann AC, **Freedberg DE**. Evolution of the environmental microbiota of a new neonatal intensive care unit and implications for infection prevention and control. *Infection Control & Hospital Epidemiology* 2020, Aug 8; 1-6. PMID: 32856577 PMCID: pending

9. Jang S, Lebwohl B, Abrams JA, Green PHR, **Freedberg DE**, Alaedini A. Celiac disease serology and gut microbiome following protein. *Medicine (Baltimore)* 2020 Aug 28;99(35): e21488. PMID: 32871870.
10. Blackett JW, Faye A, Phipps M, Li J, Lebwohl B, **Freedberg DE**. Prevalence and Risk Factors for Inappropriate Continuation of Proton Pump Inhibitors After Discharge from the Intensive Care Unit, *Mayo Clinical Proceedings*, *Accepted July 23, 2020 (print to come)*.
11. Anderson MR, Geleris J, Anderson DR, Zucker J, Nobel YR, **Freedberg DE**, Small-Saunders J, Rajagopalan KN, Greendyk R, Chae S, Natarajan K, Roh D, Edwin E, Gallagher D, Podolanczuk A, Barr RG, Ferrante AW, Baldwin MR. Body mass index and risk of intubation or death in SARS-CoV-2 infection: a retrospective cohort study. *Annals of Internal Medicine* 2020 Jul 29; M20-3214. PMID: 32726151 PMCID: PMC7397550
12. Varma S, Faye AS, Kannan A, Lawlor G, Verma A, Axelrad J, **Freedberg DE**. Patients with more severe IBD get *Clostridioides difficile* rather than *Clostridioides difficile* increasing the severity of IBD. *Digestive Diseases and Sciences*, *Accepted July 13, 2020 (print to come)*.
13. Munck C, Sheth RU, Cuaresma C, Weidler J, Stump SL, Zachariah P, Chong DH, Uhlemann AC, Abrams JA, Wang HH, **Freedberg DE**. The effect of short-course antibiotics on the resistance profile of colonizing gut bacteria in the ICU: a prospective cohort study. *Critical Care* 2020 Jul 9;24(1). PMID: 32646458 PMCID: PMC7350675
14. **Freedberg DE**, Conigliaro J, Wang, TC, Tracey KJ, Callahan MV, Abrams JA on behalf of the Famotidine Research Group. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. *Gastroenterology* 2020 May 22; 34706-5. PMID: 32446698 PMCID: PMC7242191 *Featured on cover and in accompanying editorial by Andrew Chan.*
15. Nobel YR, Phipps M, Zucker J, Lebwohl B, Wang TC, Sobieszczyk ME, **Freedberg DE**. Gastrointestinal symptoms and COVID-19: case-control study from the United States. *Gastroenterology* 2020 Jul; 159(1): 373-375. PMID: 32294477 PMCID: PMC7152871
16. **Freedberg DE**, Messina M, Lynch E, Tess M, Miracle E, Chong DH, Wahab R, Abrams JA, Wang HH, Munck C. Impact of fiber-based enteral nutrition on the gut microbiome of ICU patients receiving broad-spectrum antibiotics: a randomized pilot trial. *Critical Care Explorations* 2020 Jun 11;2(6): e0135. PMID: 32695998 PMCID: PMC7314333
17. Munck C, Sheth R, **Freedberg DE**, Harris Wang HH. Recording mobile DNA in the gut microbiota using an Escherichia coli CRISPR-Cas spacer acquisition platform. *Nature Communications* 2020 Jan 7;11(1): 95. PMID: 31911609 PMCID: PMC6946703
18. Fu Y, Moscoso DI, Porter J, Krishnareddy S, Abrams JA, Seres D, Chong DH, **Freedberg DE**. The effect of dietary fiber intake on short chain fatty acid-producing bacteria during critical illness: a prospective cohort study. *Journal of Parenteral and Enteral Nutrition* 2020, 44(3): 463-471. PMID: 31385326 PMCID: PMC7002227
19. Hung K, Knotts RM, Faye AS, Pont AR, Lebwohl B, Abrams JA, **Freedberg DE**. Factors associated with adherence to *Helicobacter pylori* testing during hospitalization for bleeding peptic ulcer disease. *Clinical Gastroenterology and Hepatology* 2020, 18(5): 1091-1098. PMID: 31352090
20. Wang Y, Schluger A, Li J, Gomme-Simmonds A, Salmasian H, **Freedberg DE**. Does addition of intravenous metronidazole to oral vancomycin improve outcomes in *Clostridioides difficile* infection? *Clinical Infectious Diseases* 2019, Epub ahead of print. PMID: 31714955
21. Faye AS, Hung K, Cheng K, Blackett JW, McKenney AS, Pont AR, Li J, Lawlor G, Lebwohl B, **Freedberg DE**. Minor hematochezia decreases use of venous thromboembolism prophylaxis in patients with inflammatory bowel disease. *Inflammatory Bowel Disease* 2019, Epub ahead of print. PMID: 31689354

22. La Carpia F, Wojczyk B, Annavajhala M, Rebbaa A, Culp-Hill R, D'Alessandro A, **Freedberg DE**, Uhlemann AC, Hod EA. Transfusional iron overload and intravenous iron infusions modify the mouse gut microbiota similarly to dietary iron. *NPJ Biofilms and Microbiomes* 2019, 5: 26. PMID: 31583109 PMCID: PMC6760189
23. Horvath A, Rainer F, Bashir M, Leber B, Schmerboeck B, Klymiuk I, Groselj-Strele A, Durdevic M, **Freedberg DE**, Abrams JA, Fickert P, Stiegler P, Stadlbauer V. Biomarkers for oralization during long-term proton pump inhibitor therapy predict survival in cirrhosis. *Scientific Reports* 2019, 9(1): 12000. PMID: 31427717 PMCID: PMC6700098
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27. Axelrad J, **Freedberg DE**, Whittier S, Greendyke W, Lebwohl B, Green D. Impact of gastrointestinal panel implementation on healthcare utilization and outcomes. *Journal of Clinical Microbiology* 2019; Epub Jan 16 ahead of print. PMID: 30651393 PMCID: pending *Selected for oral presentation at DDW 2019*
28. Wang Y, Li J, Zachariah P, Abrams JA, **Freedberg DE**. Relationship between remote cholecystectomy and incident *Clostridioides difficile* infection. *Clinical Microbiology and Infection* 2019, 25(8): 994-999. PMID: 30583059 PMCID: PMC6589130
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32. Zhou MZ, Li J, Salmasian S, Zachariah P, Yang YX, **Freedberg DE**. The local hospital milieu and healthcare-associated VRE acquisition. *J Hosp Infect* 2019; 101(1): 69-75. PMID: 30026006 PMCID: PMC6309650
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- or infection. Intensive Care Med 2018; 44(8): 1203-1211. PMID: 29936583 PMCID: PMC6309661 *Selected for oral presentation at DDW 2018*
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41. Faleck DM, Salmasian H, Furuya EY, Larson EL, Abrams JA, **Freedberg DE**. Proton pump inhibitors do not affect risk for *Clostridium difficile* infection in the intensive care unit. Am J Gastroenterol 2016; 111(11): 1641-1648. PMID: 27575714 PMCID: PMC5096970
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47. Latorre M, Lagana SM, **Freedberg DE**, Lebowitz B, Bhagat G, Lewis SK, Green PH. Endoscopic biopsy technique in the diagnosis of celiac disease: One bite or two? Gastrointest Endosc 2015; 81(5): 1228-1233. PMID: 25599173

48. **Freedberg DE**, Salmasian H, Abrams JA, Green RA. Orders for intravenous proton pump inhibitors decrease after implementation of an electronic alert. *JAMA Int Med* 2015; 175(3): 452-454. PMID: 25599173 PMCID: PMC5022559
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50. Sharaiha RZ, **Freedberg DE**, Abrams JA, Wang YC. Cost-Effectiveness of Chemoprevention with Proton Pump Inhibitors in Barrett's Esophagus. *Dig Dis Sci* 2014; 59(6): 1222-1230. PMID: 24795040
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52. **Freedberg DE**, Salmasian H, Friedman C, Abrams JA. Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection among inpatients. *Am J Gastroenterol* 2013; 108(11): 1794-1801. PMID: 24060760 PMCID: PMC3966060.
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Reviews

1. Choy A, **Freedberg DE**. Impact of microbiome-based interventions on gastrointestinal pathogen colonization in the intensive care unit. *Therapeutic Advances in Gastroenterology* 2020 Jul 17; 13. PMID: 32733601 PMCID: PMC7370550
2. Gupta A... **Freedberg DE**... Landry DW. Extrapulmonary manifestations of COVID-19. *Nature Medicine* 2020 Jul; 26(7): 1017-1032. PMID: 32651579 PMCID: pending
3. Lukovic E, Moitra VK, **Freedberg DE**. Microbiome: implications for perioperative and critical care. *Current Opinion in Anaesthesiology* 2019, 32(3): 412-420. PMID: 30925514
4. **Freedberg DE**, Kim L, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. *Gastroenterology* 2017; 152(4): 706-715. PMID: 28257716.
5. Snider E, **Freedberg DE**, Abrams JA. Potential role of the microbiome in Barrett's esophagus and esophageal adenocarcinoma. *Dig Dis Sci* 2016; 61(8): 2217-2225. PMID: 27068172
6. Latorre M, Krishnareddy S, **Freedberg DE**. Microbiome as mediator: do systemic infections start in the gut? *World J Gastro* 2015; 21(37): 10487-10492. PMID: 26457009 PMCID: PMC4588071
7. **Freedberg DE**, Lebwohl B, Abrams JA. The impact of proton pump inhibitors on the human gastrointestinal microbiome. *Clinics in Laboratory Medicine* 2014; 34(4): 771-785. PMID: 25439276 PMCID: PMC4254461

Editorials, letters, and case reports

1. Krigel A, Kong XF, **Freedberg DE**. The light at the end of the tunnel. *Gastroenterology* 2019; S0016-5085 [Epub ahead of print]. PMID 30610863

2. Bell JS, **Freedberg DE**. More data on PPI use and kidney disease. GI and Hepatology News: The official newspaper of the AGA, Nov. 8, 2017.
3. **Freedberg DE**, Abrams JA, Yang YX. Proton pump inhibitors and myocardial infarction: the current perspective. *Gastroenterology* 2015; 149(4): 830-833. PMID: 26277262
4. **Freedberg DE**, Abrams JA, Wang TC. Prevention of gastric cancer with antibiotics: can it be done without eradicating *Helicobacter pylori*? *J Natl Cancer Inst* 2014; 106(7). PMID: 24925352
5. **Freedberg DE**, Bhadelia N, Poneros JM, Oster MW. Visceral varicella in a patient with chronic lymphocytic leukemia on fludarabine: a case report. *Clin Lymphoma Myeloma Leuk* 2013; 13(1): 90-92. PMID: 23103084
6. **Freedberg DE**, Bao F, Stein JA. Rectal leiomyosarcoma after pelvic irradiation. *Clinical Gastroenterol Hepatol* 2013; 11(7): A28. PMID: 22902282
7. **Freedberg DE**. Proton pump inhibitors: a balanced view. *Practical Gastroenterology* 2013; 37(12): 44.
8. **Freedberg DE**, Husain S, Swaminath A. Severe inflammatory bowel disease-associated pyoderma gangrenosum. *Journal Gastroenterol Hepatol* 2013; 28(11): 1691. PMID: 24147454
9. **Freedberg DE**, Garcia-Carrasquillo RJ, Schwartz B, Rosenberg RM. A technique for skin-level gastrostomy tube placement after gastrostomy tube dislodgement. *Gastrointest Endosc* 2013; 78(6): 963-964. PMID: 24237952
10. **Freedberg DE**, Abrams JA. *Clostridium difficile* infection in the community: are proton pump inhibitors to blame? *World J Gastroenterol* 2013; 19(40): 6710-6713. PMID: 24187445 PMCID: PMC3812469
11. **Freedberg DE**, Abrams JA. Recent therapeutic advances in gastroenterology and hepatology. *Adv Ther* 2013; 30(10): 855-857. PMID: 24170588 PMCID: PMC3898138
12. **Freedberg DE**, Abrams JA. Does confounding explain the association between PPIs and *Clostridium difficile*-related diarrhea? *Am J Gastroenterol* 2013; 108(2): 278-279. PMID: 23381076
13. **Freedberg DE**. To eGFR or not to eGFR: here is an intern's answer. *Kidney Int* 2009; 76(2): 129-130. PMID: 19564852
14. **Freedberg DE**. Lessons from long-lived physicians. *J Am Geriatr Soc* 2006; 54(8): 1293. PMID: 16914002

Abstracts (selected)

1. Blackett WJ, Faye AS, Phipps M, Li J, Lebwohl BL, **Freedberg DE**. Inappropriate discharge on proton pump inhibitors after intensive care unit hospitalization. Digestive Disease Week, May 6, 2020 (WebEx due to COVID-19). *Selected for oral presentation and featured in AGA Today newsletter.*
2. Kuo S, Dettmer K, Annavajhala M, Uhlemann AC, Abrams JA, Oefner P, **Freedberg DE**. Urine 3-indoxyl sulfate, a gut microbiome-derived biomarker, is associated with mortality after intensive care unit admission. Digestive Disease Week, May 5, 2020 (WebEx due to COVID-19). *Selected for oral presentation.*
3. Wang Y, Salmasian H, Li J, **Freedberg DE**. Validation of peripheral eosinopenia as a novel risk factor for death in hospitalized patients with *Clostridioides difficile* infection. Digestive Disease Week, May 4, 2020 (WebEx due to COVID-19). *Selected for oral presentation.*
4. Zachariah P, Krishnamurthy G, Annavajhala MK, Moscoso DI, Rozenberg FD, Saiman L, Uhlemann AC, **Freedberg DE**. Evolution of the environmental microbiome of a new neonatal intensive care unit. Pediatric Academy of Science (PAS) 2019 Meeting, April 27, 2019, Baltimore, MD.
5. Fu Y, Moscoso DI, Porter J, Krishnareddy S, Abrams JA, Seres D, Chong DH, **Freedberg DE**. The effect of dietary fiber intake on short chain fatty acid-producing bacteria during

- critical illness: a prospective cohort study. Digestive Disease Week, May 19, 2019, San Diego, CA (selected for poster highlights tour). *Also presented at (1) AGA Gut Microbiota for Health Summit conference, March 23, 2019 in Miami, FL (winner: \$500 travel award) and (2) CUMC Medical Student Research Day, March 21, 2019 (winner: best poster award).*
6. Wang Y, Schluger A, Li J, Gomez-Simmonds A, **Freedberg DE**. Does addition of metronidazole to oral vancomycin improve outcomes in *Clostridioides difficile* infection? Digestive Disease Week, May 20, 2019, San Diego, CA. *Selected for oral presentation at Columbia Resident Research Day Grand Rounds, March 27, 2019.*
 7. Faye AS, Hung K, Blackett JW, Pont AR, Lawlor G, Lichtiger S, Lebwohl B, **Freedberg DE**. Hematochezia decreases use of venous thromboembolism prophylaxis in patients with inflammatory bowel disease. Digestive Disease Week, May 20, 2019, San Diego, CA.
 8. Wang Y, Li J, Zachariah P, Abrams JA, **Freedberg DE**. Relationship between remote history of cholecystectomy and risk for incident *Clostridium difficile* infection. American College of Gastroenterology, October 8, 2018, Philadelphia, PA.
 9. Hung K, Abdelmessih R, Faye AS, Pont AR, **Freedberg DE**. Adherence to *Helicobacter pylori* testing after hospitalization for bleeding peptic ulcer disease. American College of Gastroenterology, October 8, 2018, Philadelphia, PA. *Awarded first place honors among posters at the 42nd annual meeting of the New York Society of Gastrointestinal Endoscopy, February 6, 2019.*
 10. Zhou MZ, Li J, Salmasian S, Zachariah P, Yang YX, **Freedberg DE**. The local hospital milieu and healthcare-associated VRE acquisition. IDweek 2018, October 5, 2018, San Francisco, CA.
 11. Cohen ME, Salmasian H, MD, Li J, Liu J, Zachariah P, Wright JD, **Freedberg DE**. Surgical Antibiotic Prophylaxis is not Associated with Risk for Post-Operative Antibiotic-Resistant Infections. IDweek 2017, October 7, 2017, San Diego, CA.
 12. Mahadev S, Lebwohl B, **Freedberg DE**. Trainee colonoscopy quality is influenced by the independent performance characteristics of supervising physicians. Digestive Disease Week, May 6-9, 2017. *Selected for oral presentation.*
 13. Livanos AE, Snider EJ, Terry ME, Abrams JA, Chong DH, **Freedberg DE**. Loss of Short Chain Fatty Acid-Producing Clostridia Occurs Rapidly After ICU Admission and Associates with Receipt of Antibiotics. Digestive Disease Week, May 6-9, 2017. *Additionally selected for presentation at CUMC Medicine Grand Rounds (Clinician-Scientist Research Pathway Presentation Day, Nov 8, 2017).*
 14. Mahadev S, **Freedberg DE**. Impact of trainee experience on the decision to perform endoscopy on weekends. Digestive Disease Week, May 6-9, 2017.
 15. Snider EJ, Nobel YR, Compres G, **Freedberg DE**, Toussaint NC, Abrams JA. Oral Microbiome Alterations in Patients with Barrett's Esophagus. Digestive Disease Week, May 6-9, 2017. *Selected for oral presentation.*
 16. **Freedberg DE**, Salmasian H, Wang TC, Abrams JA. Specific hospital rooms are associated with increased risk for *Clostridium difficile* infection. Digestive Disease Week, May 6-9, 2017.
 17. **Freedberg DE**, Salmasian H, Cohen B, Abrams JA, Larson EL. Receipt of antibiotics in hospitalized patients increases risk for *Clostridium difficile* infection in future patients who occupy the same bed. IDWeek 2016, October 29, 2016, New Orleans, LA.
 18. Hathway J, Larson EL, Abrams JA, **Freedberg DE**. Exposure to antibiotics in the intensive care unit is associated with increased risk for bacteremia from enteric organisms. IDWeek 2016, October 29, 2016, New Orleans, LA.
 19. Jang S, Uhde, Indart AM, **Freedberg DE**, Alaedini A. Markers of celiac disease and immune reactivity to gluten in response to the use of proton pump inhibitors. Women in Science at Columbia Symposium, April 23, 2016. *Selected for oral presentation.*

20. Laszkowska M, Terry M, Whittier S, Abrams JA, **Freedberg DE**. Timing and Risk Factors for Gastrointestinal Acquisition of Multi-Drug Resistant Organisms in the Intensive Care Unit. Digestive Disease Week 2016, San Diego, CA. *Additionally selected for oral presentation at Columbia University Medical Center Grand Rounds on Resident Research Day, April 6, 2016.*
21. Mahadev S, Lebwohl B, Ramirez I, Garcia-Carrasquillo RJ, **Freedberg DE**. Transition to a GI Hospitalist System Is Associated With Expedited Upper Endoscopy. Digestive Disease Week 2016, San Diego, CA.
22. **Freedberg DE**, Toussaint NC, Chen SP, Ratner AJ, Whittier S, Wang TC, Wang HH, Abrams JA. Proton Pump Inhibitors Alter Specific Taxa in the Human Fecal Microbiome: Results of a Crossover Trial. Digestive Disease Week 2015, Washington, DC.
23. **Freedberg DE**, Haynes K, Denburg MR, Zemel BS, Leonard MB, Abrams JA, Yang Y. Use of Proton Pump inhibitors is Associated with Non-Osteoporotic Fractures: A Population-Based Study. Digestive Disease Week 2015, Washington, DC.
24. Margolin EJ, Hur L, Wang HH, Toussaint NC, Abrams JA, **Freedberg DE**. Impact of diet on the relationship between obesity and the colonic microbiome. Annual Eastern-Atlantic Student Research Conference 2015, Miami, FL.
25. Faleck DM, Salmasian H, Furuya Y, Abrams JA, **Freedberg DE**. Risk factors for intensive care unit-onset *Clostridium difficile* infection. American College of Gastroenterology Annual Scientific Meeting 2014, Philadelphia, PA.
26. **Freedberg DE**, Salmasian H, Abrams JA, Green RA. Intravenous proton pump inhibitor orders can be decreased with an electronic alert. American College of Gastroenterology Annual Scientific Meeting 2013, San Diego, CA.
27. **Freedberg DE**, Salmasian H, Friedman CF, Abrams JA. Proton pump inhibitor use and risk for *Clostridium difficile*-associated diarrhea among inpatients. Digestive Disease Week 2013, Orlando, FL.
28. Salmasian H, **Freedberg DE**, Abrams JA, Friedman C. An automated tool for detecting medication overuse. American Medical Informatics Association Annual Symposium 2012, Chicago, IL. *Selected for conference highlights poster session.*
29. **Freedberg DE**, Dave JK, Kurth T, Gaziano J, Bludau JHA. Cognitive impairment in the oldest old: hospitalization and mortality. American Geriatrics Society 2006 Annual Meeting, Chicago, IL. Journal of General Internal Medicine 2006; 21(4): S29-30.
30. **Freedberg DE**, Yates LB, Kurth T, Gaziano J. Self-assessment of health in nonagenarian men. American Geriatrics Society 2006 Annual Meeting, Chicago, IL. Journal of the American Geriatrics Society 2006; 54(4): S196. *Selected for the Presidential Poster Session.*

Invited oral presentations and talks (regional, national, or international)

1. Famotidine for COVID-19 (Yes, Famotidine). New York Society of Gastrointestinal Endoscopy Research Seminar: COVID-19, Data from the Epicenter (keynote address). June 2, 2020. Similar talk given May 6, 2020 for Columbia Oncology Grand Rounds; May 20, 2020 for the Mailman School of Public Health COVID-19 Virtual Symposium; June 9, 2020 for Columbia ID Grand Rounds; December 4, 2020 for the 37th Annual Columbia-Cornell Update in Gastroenterology and Hepatology.
2. Problems in large, pragmatic randomized trials in the intensive care unit. Otsuka Pharmaceuticals, Princeton, NJ, March 18, 2020.
3. Can the Gut Microbiome be Changed to Decrease Risk for Infection in the Intensive Care Unit? University of Pennsylvania School of Medicine Gastroenterology Grand Rounds, Philadelphia, PA, January 15, 2020.
4. Can the Gut Microbiome be Changed to Alter Risk for Infection? Cornell-Weill School of Medicine GI Grand Rounds, New York, NY, September 26, 2019.

5. AGA Roadmap for a Pathway for Successfully Transitioning Early-Stage Clinical-Translational Investigators to Independence. Presented with Ryan Ungaro. American Gastroenterological Association (AGA) Joint Committee Meeting, Washington, DC, September 21, 2019.
6. Causes and consequences of gut pathogen colonization in the intensive care unit. Microbiome Science, Berchtesgaden, Germany, September 21, 2018.
7. Gastrointestinal bacterial pathogen colonization and risk for subsequent infection in the intensive care unit. Digestive Diseases Week (annual meeting of the AGA), Washington, DC, June 5, 2018.
8. Longterm proton pump inhibitors: balancing the risks and benefits. Gastroenterology Grand Rounds, Icahn School of Medicine at Mt. Sinai, New York, NY, January 5, 2018.
9. Longterm proton pump inhibitors: balancing the risks and benefits. Gastroenterology Grand Rounds, Sidney Kimmel School of Medicine, Thomas Jefferson University, Philadelphia, PA, November 15, 2017.
10. Longterm proton pump inhibitors: balancing the risks and benefits. Quarterly Meeting of the Massachusetts Gastroenterology Association, Boston, MA, September 27, 2017.
11. The Role of the Microbiome in Gastrointestinal Diseases. Harvard Medical School Board Review in Gastroenterology & Hepatology, Boston, MA (recorded), June 27, 2017.
12. Infectious complications of chronic use of proton pump inhibitors. AGA clinical symposium, Digestive Diseases Week (annual meeting of the AGA), San Diego, CA, May 21, 2016.
13. Effect of proton pump inhibitors on the human colonic microbiome. Lucille Castori Workshop. Memorial Sloan Kettering Cancer Center, New York, NY, July 16, 2014.
14. Proton pump inhibitors and fracture risk in children and young adults within The Health Improvement Network (THIN): a nested case-control study. THIN Annual Research Symposium. University of Pennsylvania, Philadelphia, PA, June 4, 2014.
15. Research questions related to proton pump inhibitors. Gastroenterology Grand Rounds. Methodist Hospital, Brooklyn, NY, November 21, 2013.

Invited oral presentations and talks (local)

1. Can nutritional therapy be used to change the gut microbiome to decrease risk for systemic infection? Columbia Medical Nutrition Service Grand Rounds, May 20, 2020 (given via zoom).
2. Can the Microbiome be Changed to Decrease Risk for Infections? CUMC Division of Infectious Disease Grand Rounds, New York, NY, February 21, 2019.
3. Can Fiber Improve Outcomes Related to the Gut Microbiome in the ICU? CUMC Critical Care Grand Rounds, New York, NY, December 21, 2018.
4. How the hospital environment shapes risk for *Clostridium difficile* infection. Mailman School of Public Health, New York, NY, June 23, 2017.
5. *Clostridium difficile* infection and toxic megacolon in the intensive care unit. Neurocritical Care Grand Rounds, Columbia University Medical Center, New York, NY, June 1, 2017.
6. How the hospital environment shapes risk for *Clostridium difficile* infection. Medicine Grand Rounds (John N. Loeb annual lecture), Columbia University Medical Center, New York, NY, April 19, 2017.
7. Gut colonization with antibiotic-resistant bacteria in the intensive care unit. Critical Care Grand Rounds, Columbia University Medical Center, New York, NY, February 2, 2017.
8. Balancing the risks and benefits of long-term proton pump inhibitors. Columbia-Cornell 33rd Annual Postgraduate Update in Gastroenterology, Hepatology, and Nutrition, Columbia University Medical Center, New York, NY, December 3, 2016.
9. How the hospital environment shapes risk for *Clostridium difficile* infection. Columbia Microbiome Working Group, Columbia University Medical Center, New York, NY, November 3, 2016.
10. High yield topics in gastroenterology. 22nd Annual Update & Intensive Board Review of Internal Medicine 2016, Columbia University Medical Center, New York, NY, June 9, 2016.

11. *Clostridium difficile* infection and the gastrointestinal microbiome in the intensive care unit. Neurocritical Care Grand Rounds, Columbia University Medical Center, New York, NY, April 21, 2016.
12. Loss of Gastrointestinal Colonization Resistance in the Intensive Care Unit. Critical Care Grand Rounds, Columbia University Medical Center, New York, NY, April 14, 2016.
13. Loss of gastrointestinal colonization resistance leads to antibiotic-resistant infections in the intensive care unit. Clinical-Epidemiological Research Seminar Series. Columbia University Medical Center, New York, NY, October 1, 2015.
14. Effect of proton pump inhibitors on the fecal microbiome in children: a prospective study. Pediatric Gastroenterology Grand Rounds. Columbia University Medical Center, New York, NY, August 22, 2014.
15. Clinical and microbiome factors associated with intensive care unit-onset *Clostridium difficile* infection. Clinical-Epidemiological Research Seminar Series. Columbia University Medical Center, New York, NY, June 5, 2014.
16. Upper gastrointestinal bleeding, proton pump inhibitors, and the gastrointestinal microbiome. Medicine Rounds. Allen Hospital, New York, NY, April 22, 2014.
17. Adverse effects of proton pump inhibitors. Gastroenterology Grand Rounds. Columbia University Medical Center, New York, NY, October 1, 2012.

Original Article

Evolution of the environmental microbiota of a new neonatal intensive care unit (NICU) and implications for infection prevention and control

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Abstract

Objective: To describe changes in the environmental microbiota of a new neonatal intensive care unit (NICU) and potential implications for infection prevention and control (IPC) efforts.

Design: Prospective observational study.

Setting: A newly constructed level IV neonatal cardiac intensive care unit (NCICU) before and after patient introduction and the original NICU prior to patient transfer.

Methods: Environmental samples were obtained from the original NICU prior to patient transfer to a new NCICU. Serial sampling of patient rooms and provider areas of the new NICU was conducted immediately prior to patient introduction and over an 11-month study period. Microbiota at each sampling point were characterized using Illumina sequencing of the V3/V4 region of the 16S rRNA gene. Microbiota characteristics (α and β diversity and differential abundance) were compared based on time, location, and clinical factors (room-level antibiotic use and patient turnover).

Results: An immediate increase in the environmental differential abundance of gut anaerobes were seen after patient introduction. There was an increase in the relative abundance of *Staphylococcus* spp, *Klebsiella* spp, *Pseudomonas* spp, and *Streptococcus* spp over time. The new NCICU consistently showed more diverse microbiota and remained distinct from the original NICU. The microbiota of the provider areas of the NCICU eventually formed a cluster separate from the patient rooms. Patient turnover increased room-level microbiota diversity.

Conclusion: Microbiota characteristics of the new NICU were distinct from the original ICU despite housing similar patients. Patient and provider areas developed distinct microbiota profiles. Non-culture-based methods may be a useful adjunct to current IPC practice.

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Studies from established neonatal intensive care units (NICUs) demonstrate diverse microbiota in the built environment that surrounds neonates.¹ Exchange of organisms between the microbiota of the built environment and resident neonates has been described,² and neonates in different locations within the same hospital are colonized with location-specific microbiota profiles.³ The NICU microbial environment thus plays a role in the development of hospitalized infants' microbiota⁴ and could moderate acquisition of pathogenic organisms. However, the initial microbiota of the built environment of the NICU before patient

introduction and its evolution over time after patient introduction have not been well described.⁵

Insights as to how patient introduction may shape the built environment of hospital units have previously come from the hospital setting caring for adults.^{6,7} For example, in a large tertiary-care adult hospital, the introduction of patients was associated with an increase in skin-associated genera (eg, *Corynebacterium*, *Staphylococcus*, and *Streptococcus*, with concurrent decreases in the abundance of *Acinetobacter* and *Pseudomonas*), which had dominated samples prior to opening.⁸ Describing the built environment of a NICU prior to introducing patients, and its evolution over time would help better delineate the NICU built environment–neonate interaction and could potentially help assess the effectiveness of routine infection prevention and control (IPC) practices in controlling colonization in the built environment over time.

In this study, we used the opening of a new neonatal cardiac intensive care unit, (NCICU) to describe the microbiota of the built

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environment prior to admitting patients and periodically after patient introduction. We compared microbial community changes over time within the new NCICU and between the new NCICU and the microbiota of the built environment of the previous NICU within the same hospital, which housed the same patients prior to transfer. We hypothesized that (1) the built-environment microbiota of the new NCICU would gradually become similar to that of the built environment of the previous NICU location and (2) that specific clinical variables such as antibiotic use and patient turnover would have a measurable impact on the microbiota of the built environment in the new NCICU.

Methods

Study design

This was an 11-month prospective longitudinal study carried out at NewYork-Presbyterian Morgan Stanley Children's Hospital, a 200-bed academically affiliated tertiary-care hospital. Two geographically separate locations in the same hospital were included in built-environment surveillance: the original 50-bed NICU, and a newly constructed 17-bed NCICU. On September 27, 2017, the existing NICU transferred some patients to the new NCICU. The Columbia University Irving Medical Center Institutional Review Board approved this study with a waiver of informed consent.

Environmental sampling strategy

Samples from the built environment were collected from 7 patient rooms in the original NICU housing cardiac patients the day before infants were transferred to the new NCICU. On the same day, samples were collected from 5 empty patient rooms and 1 common staff area in the new NCICU; simulations had been performed in the new NCICU during the weeks prior to patient transfer. Samples from these same locations were then collected from the new NCICU over an 11-month period, approximately doubling the time interval between each sample collection: new NCICU days 1, 5, 9, 16, 33, 61, 89, and 304. This sampling frequency was adopted to be more sensitive to early shifts in the built-environment microbiota while reducing the burden of sample collection and analysis.

Built environment sampling procedure

Specific surfaces were targeted for sampling in each patient room in both the original and the new units. These surfaces were determined a priori in collaboration with IPC personnel based on past outbreak investigations and surveillance efforts because they were the most commonly contaminated, as determined by bacterial cultures. Surfaces within a room were swabbed using a single, large, sponge-type swab (3M Product ID no. 70200750951). This technique, which combined multiple surfaces, was done to increase total microbial content gathered from each room and to improve the signal-to-noise ratio within each sample.² In each room, each surface was swabbed for 2–3 minutes each in the following order: bedrails and surfaces of isolettes, monitors, and infusion pump high-touch surfaces, inside door handles, and diaper scales. This order was selected so that the surfaces closest to the baby were swabbed first, successively moving to surfaces that were likely to have greater bacterial density. We also collected swabs from the common provider workplace area where the surfaces included countertops, computer mouse and keyboard, and chair armrests.

Sample processing and cultures

After collection, swabs were squeezed and drained for 1 minute to yield 2.5 mL of fluid. Aerobic cultures were also performed for (1) vancomycin-resistant *Enterococcus* (VRE), (2) methicillin-resistant *Staphylococcus aureus* (MRSA) (Remel), and (3) multidrug-resistant gram-negative rods using Chromagar. These samples were then stored frozen at -80°C for batched DNA extraction and subsequent 16S rRNA sequencing of microbial DNA.

Infection prevention and antibiotic practices in the new NCICU

According to prior established IPC policy, routine cleaning and disinfection of the NCICU was performed twice daily using disposable wipes and a bleach-based product throughout the study period. Environmental surfaces and points of patient or healthcare worker contact were targeted during daily cleaning. Upon patient discharge or transfer between locations, an additional terminal cleaning was performed, which included removal of curtains, remaining supplies, ventilators, and any residual patient care equipment. The neonatal isolettes are exchanged every 14 days and are cleaned at a dedicated equipment center. Empiric antibiotic use protocols and hand hygiene compliance in both the NICU and NCICU were reviewed for differences and were noted if present.

Sequencing and microbiota analysis

DNA was extracted using the Qiagen AllPrep PowerViral DNA/RNA Kit. The V3/V4 region of the 16S rRNA gene was amplified using established primers⁹ with Illumina Nextera adaptors. Libraries were multiplexed using Illumina Nextera XT Index kits and were normalized and pooled with 10% PhiX. Sequencing was performed on an Illumina MiSeq platform (MiSeq Reagent kit v3, 600 cycles). 16S rRNA sequences were processed using QIIME for quality-filtering, trimming, dereplication, and chimeric sequence filtering of FASTQ sequences through the National Institute of Allergy and Infectious Diseases Nephel platform.¹⁰ In total, 61 samples were sequenced, and 60 of these samples passed the minimum read cutoff of 7,500 reads for inclusion in further analysis. Low-abundance operational taxonomic units (OTUs) with relative abundance $<0.005\%$ were filtered out using the R package phyloseq v1.28.0.¹¹ Clustering of filtered reads into OTUs at 97% similarity was performed. The Greengenes 97% database was used as a reference database for taxonomic classification of these OTUs.¹²

Relative abundances of specific taxa were calculated and compared between the original and new units, as well as across time in the new unit. The pipeline used in this study, DESeq2, uses a generalized linear model to analyze log 2 fold changes in differential abundance. The Wald test was used for significance testing with adjustment for multiple testing using the Benjamini and Hochberg test.¹³ Principal coordinate analysis of weighted UniFrac β diversity was used to assess overall similarity between samples collected based on (1) the date of collection and (2) the geographical location of the samples within the NCICU.

The Chao index was used to quantify α diversity, which was compared between the original and the new NICUs. We determined the correlation of changes in room-specific α diversity between sampling time points and 2 room-level clinical exposures of interest: (1) interval broad-spectrum antibiotic use, and (2) interval patient turnover using samples obtained during the last

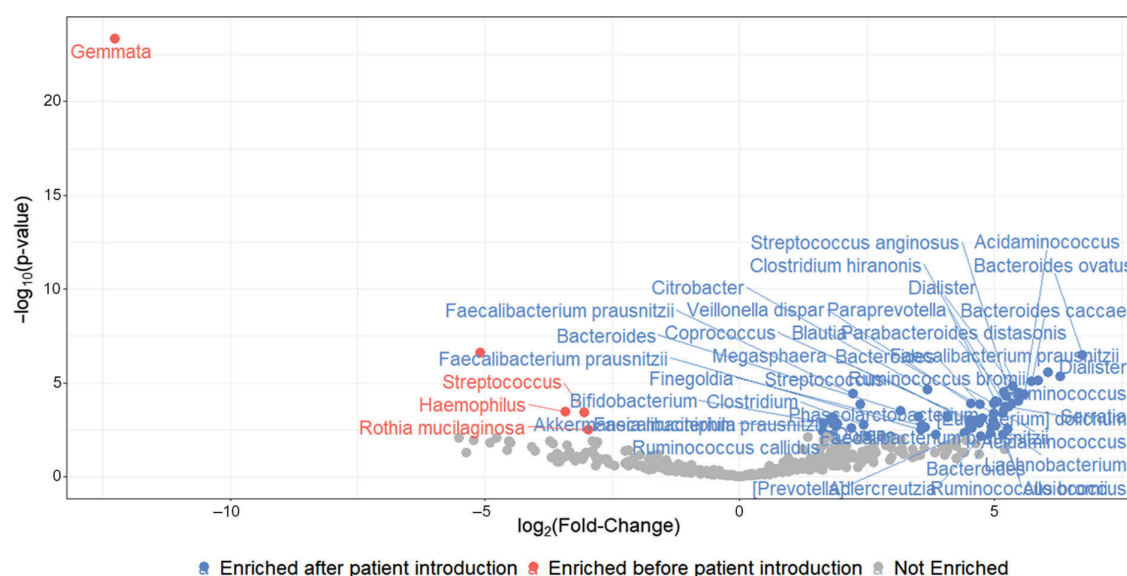


Fig. 1. Volcano plot demonstrating changes in relative taxon abundance between baseline and immediately after patient introduction.

4 sampling points (ie, days 33, 61, 89, and 304). Interval antibiotic use was defined as the number of days of broad-spectrum antibiotics administered to patients in that specific location between the sampling time points divided by the number of interval days. Broad-spectrum antibiotic use was defined as treatment with any systemic third- or fourth-generation cephalosporin, vancomycin, piperacillin/tazobactam, linezolid and/or aminoglycoside. Interval patient turnover was defined as the total number of occupant changes that occurred between sampling time points divided by the number of interval days.

Results

Taxa changes in new NCICU with patient introduction

Prior to patient introduction into the new NCICU, multiple taxa were detected in the built environment including taxa of potential clinical importance: *Staphylococcus* spp, *Klebsiella* spp, *Pseudomonas* spp, and *Streptococcus* spp. Only 1 taxon (*Gemmata*) was present in the built environment prior to patient introduction but was not detected after patient introduction. There was an immediate change in the overall differential abundance of taxa on the first day of patient introduction, with increases in gut-related anaerobes, (*Bacteroides*, *Bifidobacterium*, *Ruminococcus*, and *Faecalibacterium*) being most striking (Fig. 1). Over time, there was an increase in differential abundance of *Staphylococcus*, *Enterobacteriaceae*, *Pseudomonas*, and *Enterococcus* (Fig. 2).

Microbiota dissimilarity across time and geographic location

The built-environment microbial communities from locations in the original NICU remained distinct from locations in the new NCICU at all study time points (Fig. 3). The microbiota of the previous NICU location just prior to patient transfer was characterized by an abundance of *Pseudomonas* OTUs. The common staff areas in the new NCICU were initially closer to the microbiota profiles of patient rooms, but over time these microbiota profiles diverged toward a distant distinct cluster that aligned closer with that of the original NICU; both were dominated by *Pseudomonas* (Fig. 3).

Changes in alpha diversity in the new NCICU

Mean α diversity (Chao index) was lowest in the former NICU (mean $\pm$ SD, 402 $\pm$ 166). The mean α diversity of the new location immediately after patient introduction was significantly higher (1,003.02 $\pm$ 127.96; $P = .045$) and stayed higher compared to the original NICU over the 11 months of the study (969.63; $P < .01$).

Correlation of cumulative antibiotic use and patient turnover with alpha diversity of the built environment of patient rooms in the new NICU

Interval increases in patient turnover increased microbial diversity (correlation coefficient of 0.39), and the impact of room-level antibiotic use on α diversity was limited (correlation coefficient of -0.05) (Fig. 4).

Routine bacterial cultures

In total, 61 cultures were processed. All were negative for the targeted drug-resistant bacteria, except cultures from the common provider area were positive for *Acinetobacter baumannii* and *Acinetobacter iwoffii* on Day 89.

Discussion

In this pilot study of microbiota of the built environment of a new NCICU, we demonstrated time-dependent changes with implications for assessing IPC practice. The data from these methods could help hospital epidemiologists (1) understand global changes in the patient environment secondary to a disruptive change, (2) define and contrast microbiologic niches within a specific unit to monitor compliance with IPC practice, and (3) identify routes of transmission of organisms within the hospital environment.

First, even prior to the introduction of patients, diverse microbiota including taxa of clinical importance were detected in the built environment. The initial microbiota profile was disrupted almost immediately with patient introduction. The most noticeable change with patient introduction was an increase in anaerobic organisms which have been associated with the neonatal gut.¹⁴ While not unexpected, the immediacy of the change was striking

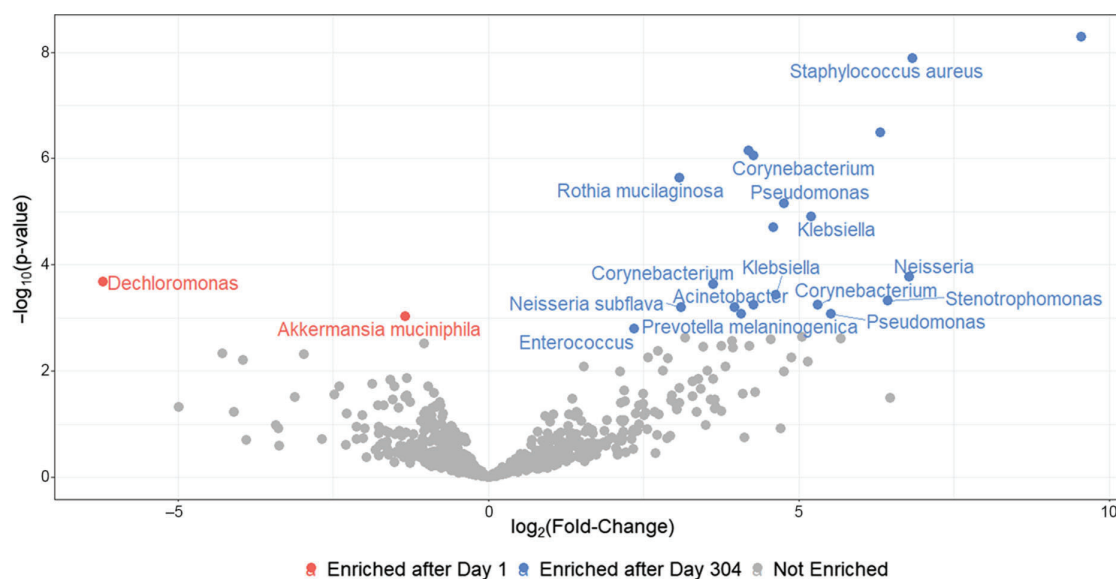


Fig. 2. Volcano plot demonstrating changes in relative taxon abundance between baseline and at end of study period.

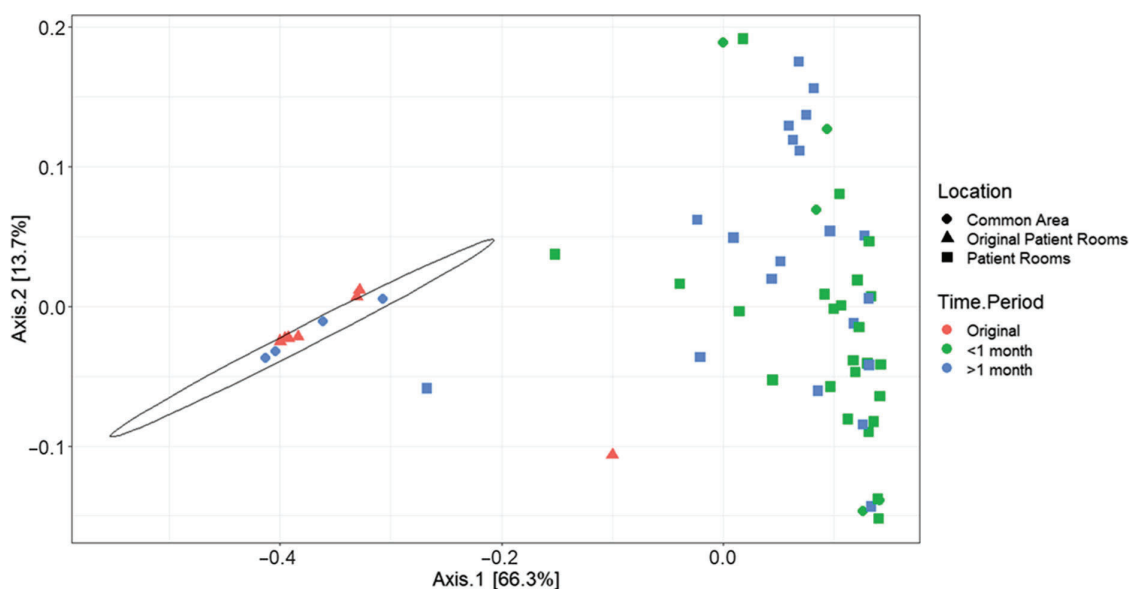


Fig. 3. The β diversity plots demonstrating clustering of samples across time and location. In the later period, samples collected from the common area cluster together with samples from the original NICU. The circle is an ellipse assuming multivariate t distribution drawn around the samples from the common area over 1 month after patient introduction.

and implies that patients' impact on the environment could outpace routine IPC interventions. Over time, after patient introduction, clinically relevant organisms, such as *Enterobacteriaceae*, *Pseudomonas*, and *Staphylococcus*, occupied a larger fraction of the microbiota of the built environment of patient rooms. This gradual increase occurred despite IPC activities designed to mitigate patient-to-environment transfer: daily cleaning, terminal cleaning, and barrier precautions for patients with MDROs. The scope of these changes were not identified using routine surveillance and indicate the potential benefit of molecular methods in identifying rapid changes in a local environment prior to being reflected in clinical or environmental cultures.

The dominance of the ICU built environment with these hospital-specific organisms has been demonstrated previously.¹⁵ Possible explanations for this preferential organism burden include the cumulative pressure of local antibiotic use, organism propensity to create biofilms resistant to regular cleaning practices,¹⁶ or a continued reservoir of organisms contributed by healthcare providers. Across all time points, however, the built environment of the NCICU remained distinct from the original location. The original NICU was characterized by a low-diversity state seen in established ICU-type settings.¹⁷ Our findings thus illustrate the difference that altering the physical location makes to the microbiota of the patient environment within the same

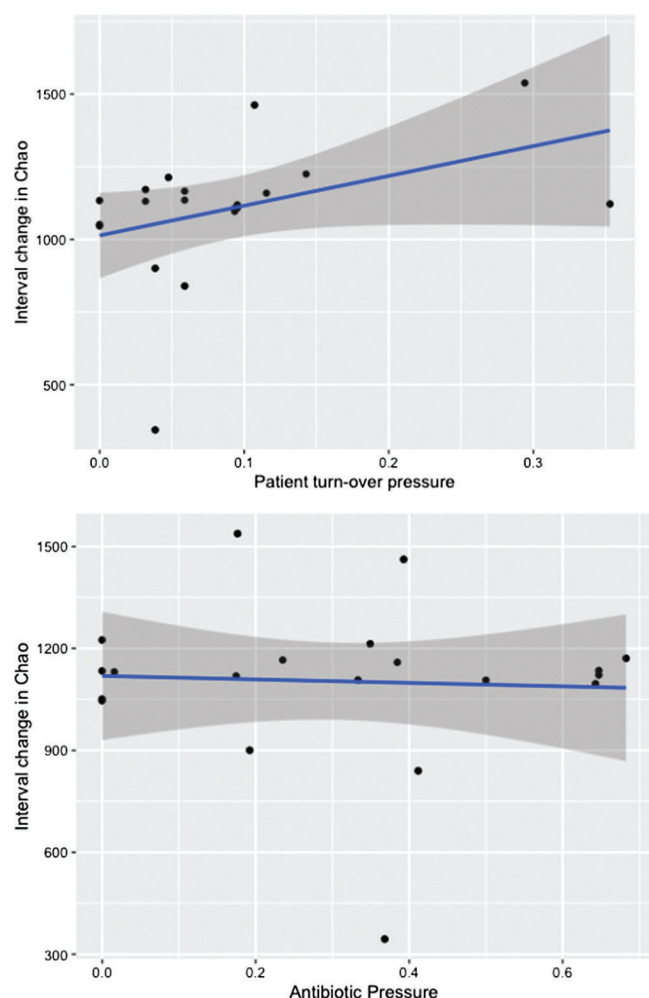


Fig. 4. Changes in α diversity (Chao index) against interval number of occupants and interval antibiotic use. Both variables were normalized for interval days.

hospital, at least in the short term, which is consistent with previous work.³

The microbiota of the common area of the NCICU, frequented by providers, initially resembled patient areas. However, the common area eventually formed a separate cluster. This dissimilarity between patient and provider areas is a desirable outcome from an infection control perspective, indicating limited transfer of organisms from patient rooms to shared areas. Distinct microbiota niches within the hospital environment have been described in adult settings.^{6,8} Correlating these separate profiles with relevant IPC practice could help monitor compliance.

Interestingly, microbiota profiles of common staff areas of the new NCICU quickly became similar to those of the original NICU with a high dominance of *Pseudomonas*. Some providers staff both units, which could contribute to this finding. Whether provider work stations act as reservoirs for typical hospital associated pathogens across hospital units either because of traffic, suboptimal cleaning, or proximity to *Pseudomonas* reservoirs (eg, sinks) should be further studied. This finding also illustrates the application of these techniques to identify routes of transmission between areas based on similarity between microbiota profiles.

The microbiota in the rooms in the new NICU remained mostly similar over time. The impact of modifiable factors, such as antibiotic use on the microbiota, was limited. The limited impact of

antibiotic use observed could be because of the relatively short study duration, long hospital stays, and relatively low rates of broad-spectrum antibiotic use compared to adult units.¹⁸ In contrast, a positive association with increased diversity was observed with patient turnover, suggesting that influx of new patients and interval terminal cleanings may help reset microbial diversity.

This study has several limitations. The sample size was small, and our patient population was restricted to neonates with complex cardiac issues, which limits the generalizability of our findings. Species-level identification was not available for all taxa, so the attribution of potential clinical significance may not be fully accurate. Routine cultures were mostly negative, so viability of organisms could not be ascertained. Multidrug-resistant organisms were not isolated in the environment, which may limit generalizability. The lack of identification of antibiotic resistance using molecular methods limits inference around the impact of antibiotic use. This study was limited by a lack of a quantitative measure of bioburden. Due to our swabbing technique, we were unable to distinguish between surfaces sampled within each room. Also, we did not sample patients or healthcare workers which limits inference about transmission.

In summary, the introduction of patients into the hospital environment, leads to time-dependent and clinical care-dependent changes in the resident microbiota. Patient turnover may influence the overall structure of the microbiota in the built environment. Non-culture-based methods to track environmental microbiota may reveal patterns of transmission and colonization missed by regular cultures and may be a useful adjunct to current IPC practice.

Acknowledgments. None.

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Conflicts of interest. All authors report no conflicts of interest relevant to this article.

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Associations between urinary 3-indoxyl sulfate, a gut microbiome-derived biomarker, and patient outcomes after intensive care unit admission

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ABSTRACT

Purpose: 3-indoxyl sulfate (3-IS) is an indole metabolism byproduct produced by commensal gut bacteria and excreted in the urine; low urinary 3-IS has been associated with increased mortality in bone marrow transplant recipients. This study investigated urinary 3-IS and patient outcomes in the ICU.

Materials and methods: Prospective study that collected urine samples, rectal swabs, and clinical data on 78 adult ICU patients at admission and again 72 h later. Urine was analyzed for 3-IS by mass spectrometry.

Results: Median urinary 3-IS levels were 17.1 $\mu\text{mol}/\text{mmol}$ creatinine (IQR 9.5 to 26.2) at admission and 15.6 (IQR 4.2 to 30.7) 72 h later. 22% of patients had low 3-IS ($\leq 6.9 \mu\text{mol}/\text{mmol}$) on ICU admission and 28% after 72 h. Low 3-IS at 72 h was associated with fewer ICU-free days (22.5 low versus 26 high, $p = 0.03$) and with death during one year of follow-up (36% low versus 9% high 3-IS, $p < 0.01$); there was no detectable difference in 30-day mortality (18% low versus 5% high, $p = 0.07$).

Conclusions: Low urinary 3-IS level 72 h after ICU admission was associated with fewer ICU-free days and with increased one-year but not 30-day mortality. Further studies should investigate urinary 3-IS as an ICU biomarker.

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1. Introduction

In patients who are critically ill, the normal microbiome is disrupted, leading to loss of gut colonization resistance and expansion of disease-promoting pathogens [1,2]. This “dysbiosis” has been shown to be a risk factor for nosocomial infections, sepsis, multiple organ dysfunction, and increased mortality [3–5]. Fecal microbial diversity has been used as a surrogate for colonization resistance and low fecal biodiversity has been associated with increased risk for death and infection, most notably in bone marrow transplant recipients [3,6].

In the intensive care unit (ICU), fecal microbial diversity is low at admission, and the microbiome becomes dominated by pathogens

including *Enterococcus* and Gram negative bacteria [2,7]. Downstream, ICU patients who are colonized with enteric pathogens have increased risk for death or infection [8]. It would be important to rapidly identify patients with dysbiosis in order to develop clinical strategies to help augment commensal microbes, restore diverse flora, and prevent loss of colonization resistance. Currently, a major challenge facing such strategies is that it is difficult or impossible to rapidly identify the patients at highest risk of dysbiosis within the diverse ICU population [4]. There are no tests for clinical features that clearly identify patients likely to benefit from microbiome-based interventions.

3-indoxyl sulfate (3-IS) is an indole metabolism byproduct produced by bacteria expressing tryptophanase and has been shown to be an important intercellular signal in microbial communities [9] and may support the survival of mixed microbial communities [10]. In the bone marrow transplant population, low levels of urinary 3-indoxyl sulfate were associated with higher transplant-related mortality and worse overall survival [11]. Since urinary 3-IS levels can be rapidly measured, it may be useful as a biomarker for gut dysbiosis in other high-mortality populations. This study sought to evaluate the utility of

Abbreviations: 3-indoxyl sulfate, 3-IS; bone marrow transplant, BMT; intensive care unit, ICU; sequential organ failure assessment, SOFA.

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urinary 3-IS levels as a gut-specific biomarker and to investigate its ability to predict outcomes in a diverse ICU population.

2. Material and methods

2.1. Study population

This was a prospective, single-center study that included consecutive adults ≥ 18 years old who were newly admitted to any one of the 5 medical or surgical ICUs and could be reached within 4 h of ICU admission and 72 h later. Assessments at both ICU admission and 72 h later were required in order to examine the dynamic changes in 3-IS over time. Patients were included if a urine specimen was obtained at the 72-h assessment, even if no urine was available during the initial assessment. In order to limit the population to ICU patients with a gut microbiome that was relatively preserved at the time of admission, patients were excluded if they had prior *Clostridioides difficile* infection within 90 days, bacterial bloodstream infections within 30 days, or ICU admissions within 30 days. Informed consent was obtained from all subjects or their appropriate surrogates when the patients lacked capacity. The default consent was written, but verbal surrogate consent was accepted when subjects lacked capacity and the appropriate surrogate was not available in person [12]. The institutional review board of Columbia University Medical Center approved this study.

2.2. Sample and data collection

Patients were enrolled from February 2015 to August 2018. Rectal swab and urine specimens were collected within 4 h of ICU admission with a second set of specimens collected 72 h later (± 4 h). At ICU admission and 72 h later, 8 mL of urine was taken via the collection port of an indwelling catheter that had previously been placed. A deep rectal flocked nylon swab (Copan Diagnostics, Murrieta, CA) was collected at each time point. Demographic information, laboratory data and data regarding the interventions performed in between sample collections was extracted from the electronic medical record. Data was collected as the worst clinical and laboratory values during the preceding 24 h of each sample collection time, in order to calculate the sequential organ failure assessment (SOFA) score for each subject at each time point [13]. Information for interventions performed between sample collection time points included antibiotic use (any dose or duration), proton pump inhibitor use, mechanical ventilation, hemodialysis (intermittent or continuous), immunosuppression use, opioid use, and enteral feeding (by mouth or by naso-enteric tube).

2.3. Urinary 3-indoxyl sulfate

Urinary levels of 3-IS were analyzed as both a categorical and continuous variable. Based on the cutoffs used in a prior study analyzing urinary 3-IS in the bone marrow transplant population, patients were classified as low 3-IS at levels ≤ 6.9 $\mu\text{mol}/\text{mmol}$ creatinine and as high 3-IS if levels were > 6.9 $\mu\text{mol}/\text{mmol}$ creatinine [11]. Urinary 3-IS was measured on an Agilent 1200 SL HPLC system with a 4000 QTrap mass spectrometer and a TurboV electrospray ion source using stable isotope-labeled internal standards and stock solutions as previously described [14]. Within-individual change was calculated as 3-IS after 72 h divided by 3-IS at ICU admission.

2.4. 16S rRNA gene sequencing

Swabs were sequenced at two centers because the study evolved slowly, over more than two years. For the first batch of samples, polymerase chain reaction was performed targeting the V4 hypervariable region of the 16S ribosomal RNA gene with primers from the human microbiome project. For the second batch, V3-V4 sequencing was performed using standard Illumina primers. To combine datasets for

downstream analyses, paired-ended V3-V4 reads were trimmed using BBMap to isolate the V4 region, and all sequences were then imported into QIIME2 [15]. The single-ended DADA2 pipeline was used to cluster sequences into sequence variants (SVs) which were assigned taxonomic classifications based on a naïve Bayesian approach trained on the GreenGenes 97% clustered database. A minimum threshold of 10,000 counts per sample was set for inclusion in our analysis. Exported BIOM and reconstructed phylogenetic tree files from QIIME2 were imported into R using the phyloseq package to calculate α -diversity metrics (Shannon diversity index) [16]. These metrics focused on the Shannon index, which was calculated as $-\sum_{i=1}^R p_i \log p_i$ where p is the relative abundance of each operational taxonomic unit based on 16S sequencing. Using phyloseq, an unsupervised analysis was performed to assess for any differences in the microbiome, comparing those with low versus those with high urinary 3-IS. False discovery adjusted p -value of < 0.05 was considered statistically significant in this analysis.

2.5. Statistical approach

Urinary 3-IS was measured at both ICU admission and at 72 h, but the analyses focused on 72 h 3-IS based on the rationale that the trajectory of 3-IS would be more important than its value at the moment of ICU admission. The primary outcome was mortality after ICU admission, assessed as 30-day mortality and one-year mortality gathered through hospital records, which interface with the social security death index. Other outcomes investigated were ICU-free days and culture proven infections within 30 days of ICU admission, which were determined as previously described [8]. ICU-free days were calculated as 30 days minus the number of days in the ICU, and patients were given a score of 0 if they died while in the ICU [17]. Comparisons of clinical and laboratory data were performed using Wilcoxon ranksum tests and χ^2 tests. For multivariable analysis, logistic regression modeling was used with one-year mortality as the primary outcome. A multivariable model was built to assess the independent relationship between 3-IS and mortality after adjusting for the presence of sepsis and the SOFA score, with those co-variables selected a priori as the most likely predictors of death. All statistical analysis was performed using Stata 15 (StataCorp, College Station, TX) at the alpha 0.05 level of significance.

3. Results

3.1. Urinary 3-indoxyl sulfate

A total of 78 patients met study criteria and were analyzed (Fig. 1). Median urinary 3-IS level at ICU admission was 17.1 $\mu\text{mol}/\text{mmol}$ (IQR 9.5 to 26.2) and 72 h after ICU admission was 15.6 $\mu\text{mol}/\text{mmol}$ (IQR 4.2 to 30.7). Thirteen patients were included in the analysis who had a 72 h urine sample, but for whom no admission urine sample was available.

3.2. Clinical characteristics

Baseline characteristics at ICU admission are shown in Table 1 and are stratified by urinary 3-IS levels at 72 h after admission. There were 22 patients (28%) that had low urinary 3-IS levels compared to 56 patients (72%) that had high levels at the second time point. The majority of patients were admitted to the ICU for sepsis (37%), post-surgical procedure (27%), or after a cardiac event or procedure (18%). Among those with low urinary 3-IS levels, there was a larger proportion of females (59% low 3-IS versus 30% high, $p = 0.02$). Sepsis was a more common reason for admission among patients with low urinary 3-IS levels at 72 h (77% low 3-IS versus 21% high, $p < 0.01$). At 72 h after ICU admission, patients with low urinary 3-IS levels had a median SOFA score of 6 (IQR 2 to 12) and those with high 3-IS levels had a median SOFA score of 3 (IQR 1 to 7, $p < 0.01$). SOFA components are detailed in Table 2. Patients with low 3-IS levels at 72 h, had significantly lower values of

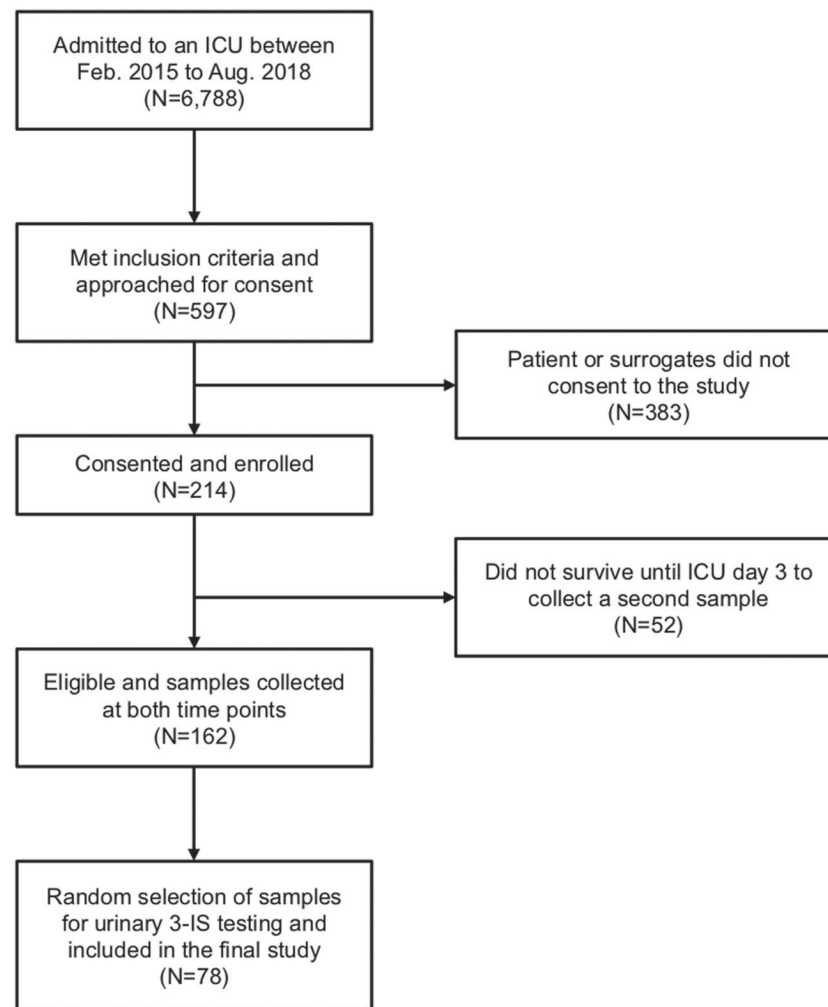


Fig. 1. Enrollment flowchart.

Table 1
Baseline patient characteristics, stratified by urinary 3-IS level 72 h after ICU admission.

Characteristics at ICU admission	Low 3-IS at 72 h (N = 22)	High 3-IS at 72 h (N = 56)	p-value
Age in years (tertiles)			0.64
30–59	6 (27%)	20 (36%)	
60–70	9 (41%)	17 (30%)	
70–90	7 (32%)	19 (34%)	
Gender			0.02
Male	9 (41%)	39 (70%)	
Female	13 (59%)	17 (30%)	
Reasons for admission			<0.01
Sepsis	17 (77%)	12 (21%)	
Surgical procedure	3 (14%)	18 (32%)	
Cardiac	0 (0%)	14 (25%)	
GI bleed	2 (9%)	3 (5%)	
Neurologic	0 (0%)	5 (9%)	
Other	0 (0%)	4 (7%)	
Charlson Comorbidities ^a			0.25
0–1 points	4 (18%)	21 (37%)	
2–3 points	10 (45%)	21 (37%)	
4+ points	8 (36%)	14 (25%)	
SOFA score			0.50
0–4 points	9 (41%)	23 (41%)	
5–8 points	8 (36%)	14 (25%)	
≥9 points	5 (23%)	19 (34%)	
Hematocrit at admission	28.8 (24.3–36.7)	34.5 (28.6–40)	0.09
Albumin at admission	3.1 (2.5–3.8)	3.6 (2.9–3.9)	0.22

3-IS: 3-indoxyl sulfate; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment score.

^a Modified Charlson's Comorbidity Index.

Table 2

Sequential Organ Failure Assessment score characteristics 72 h after ICU admission, organized by urinary 3-IS levels 72 h after ICU admission.

SOFA characteristics 72 h after ICU admission	Low 3-IS at 72 h (N = 22)	High 3-IS at 72 h (N = 56)	p-value
Median SOFA score (IQR)	6 (2–12)	3 (1–7)	p < 0.01
Total SOFA score			0.21
0–2 points	6 (27%)	26 (46%)	
3–6 points	6 (27%)	15 (27%)	
7–24 points	10 (45%)	15 (27%)	
PaO ₂ /FiO ₂			0.10
≥400	12 (55%)	40 (71%)	
300–399	3 (14%)	3 (5%)	
200–299	4 (18%)	12 (21%)	
100–199 and mechanically ventilated	2 (9%)	0 (0%)	
<100 and mechanically ventilated	1 (5%)	1 (2%)	
Platelets, ×10 ³ /μL			0.03
≥150	10 (45%)	34 (61%)	
100–150	1 (5%)	13 (23%)	
50–99	5 (23%)	5 (9%)	
20–49	5 (23%)	3 (5%)	
<20	1 (5%)	1 (2%)	
Glasgow Coma Scale			0.06
15 points	10 (45%)	36 (64%)	
13–14 points	0 (0%)	4 (7%)	
10–12 points	4 (18%)	2 (4%)	
6–9 points	2 (9%)	7 (13%)	
<6 points	6 (27%)	7 (13%)	
Bilirubin, mg/dL			<0.01
<1.2	14 (64%)	42 (75%)	
1.2–1.9	1 (5%)	10 (18%)	
2.0–5.9	6 (27%)	1 (2%)	
6.0–11.9	0 (0%)	1 (2%)	
≥12.0	1 (5%)	2 (4%)	
Mean arterial pressure or vasoactive agents			0.51
No hypotension			
MAP <70 mmHg	10 (45%)	35 (63%)	
Dopamine ≤5 or phenylephrine <0.3	5 (23%)	11 (20%)	
Dopamine >5 or norepinephrine ≤0.1 or phenylephrine >0.3	0 (0%)	1 (2%)	
Dopamine >15 or norepinephrine >0.1	5 (23%)	7 (13%)	
Creatinine, mg/dL or urine output			0.27
<1.2	7 (32%)	31 (55%)	
1.2–1.9	6 (27%)	13 (23%)	
2.0–3.4	3 (14%)	5 (9%)	
3.5–4.9 or UOP <500 mL/day	2 (9%)	4 (7%)	
≥5.0 or UOP <200 mL/day	4 (18%)	3 (5%)	

IQR: interquartile range; MAP: mean arterial pressure; UOP: urine output.

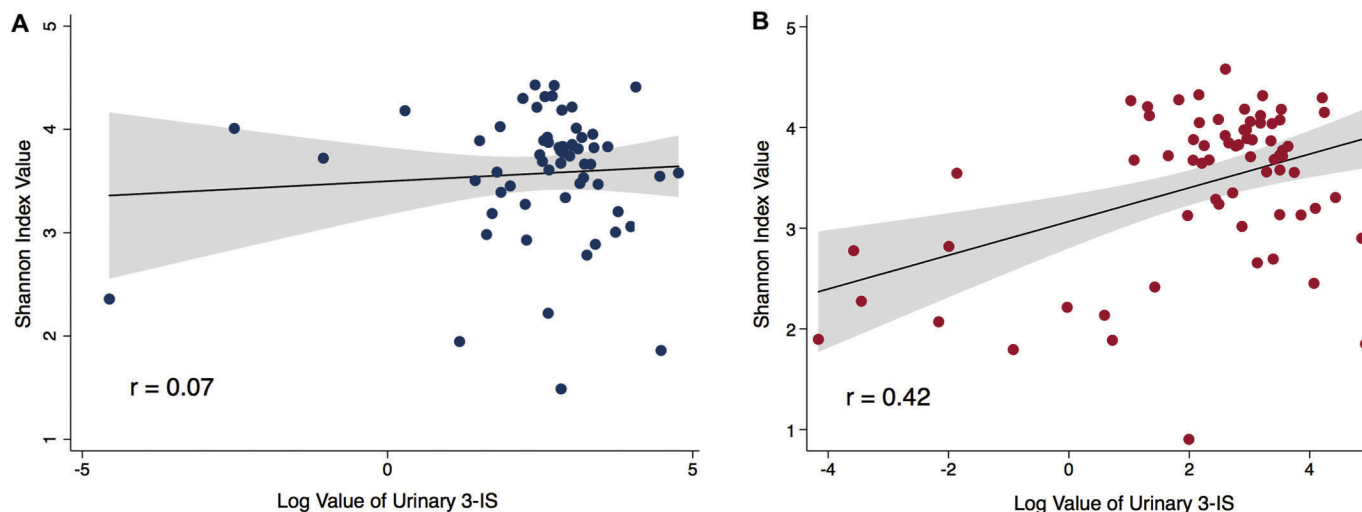
**Fig. 2.** Correlations between log urinary 3-IS and Shannon Index. Pearson correlations between log urinary 3-IS and Shannon Index at ICU admission (A) and 72 h later (B). 60 out of 78 patients had adequate data for both urinary 3-IS and Shannon Index at ICU admission, whereas 69 out of 78 were available 72 h later.

Table 3

Within-individual change in 3-IS, organized by ICU interventions.

Intervention Type	Without intervention Median (IQR)	With intervention Median (IQR)	p-value
Antibiotics ^a			
Before (N = 49)	0.82 (0.39–1.16)	1.05 (0.52–1.60)	0.54
After (N = 56)	0.61 (0.4–0.100)	1.04 (0.52–1.54)	0.45
Any (N = 58)	0.61 (0.39–1.00)	1.04 (0.52–1.60)	0.39
Immunosuppression ^b	1.08 (0.57–1.67)	0.62 (0.26–1.16)	0.04
Proton pump inhibitors	0.87 (0.39–1.23)	1.06 (0.55–1.97)	0.31
Opioids	0.69 (0.36–1.88)	1.03 (0.55–1.44)	0.48
Feeding ^c	0.94 (0.27–1.59)	1.01 (0.42–1.44)	0.86
Hemodialysis	1.01 (0.39–1.46)	0.81 (0.65–2.24)	0.42

^a Antibiotics received before ICU admission, after ICU admission for the next 72 h and any antibiotics received prior or after ICU admission.^b Immunosuppression was defined as chemotherapy or prednisone (>5 mg/day dose), cellcept, tacrolimus/everolimus/sirolimus, azathioprine, infliximab or adalimumab.^c Includes both tube feeds and ad-lib diets.

platelets and higher values of bilirubin compared to those with high 3-IS levels.

3.3. Relationship with microbiome features

The Shannon index was also analyzed for both time points and used as a surrogate for fecal microbial diversity. At ICU admission, median Shannon Index was 3.75 (IQR 3.4 to 3.9) and 72 h after was 3.71 (IQR 3.1 to 4.0). Those classified as low 3-IS levels at the second time point also had a lower Shannon Index at 72 h compared to those with high 3-IS levels (2.78 versus 3.79, $p = 0.02$). At both time points, there was a weak positive correlation between log urinary 3-IS and Shannon Index, which was statistically significant at the second time point ($r = 0.42$ $p < 0.01$) (Fig. 2A and B). Patients with high urinary 3-IS at 72 h had rectal swabs significantly enriched in sequences assigned to *E.coli* and *Parabacteroides* (both log2-fold change >20 $p < 0.01$).

3.4. Impact of ICU interventions on urinary 3-indoxyl sulfate

The impact of ICU interventions on urinary 3-IS levels was studied by analyzing within-individual change in urinary 3-IS (Table 3). Antibiotic use, both before ICU admission and between the two time points was not associated with a significant difference in levels of urinary 3-IS. Urinary 3-IS levels were significantly lower in those that were exposed to immunosuppression during the first 72 h in the ICU compared to those that were not (1.08 fold change versus 0.62 fold change, $p = 0.04$).

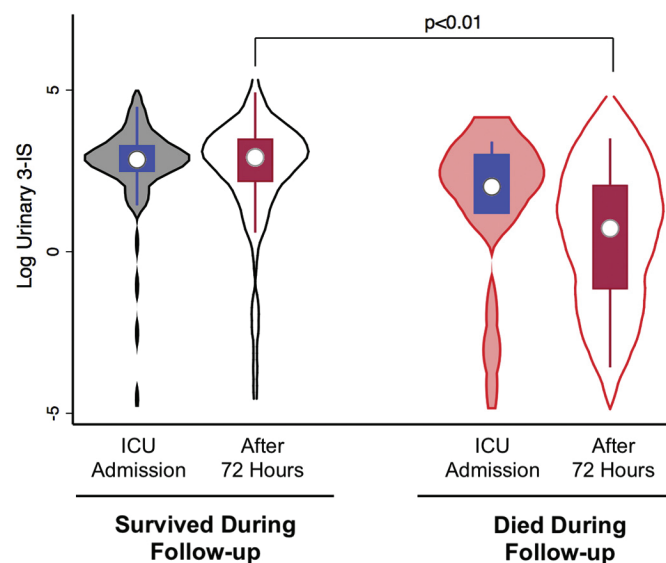


Fig. 3. Violin plot showing urinary 3-IS change. Log urinary 3-IS levels at time of ICU admission and 72 h later, stratified by survival outcome at one year.

There was no difference in change within urinary 3-IS when patients were exposed to proton pump inhibitors, opioids, feeding or hemodialysis between the two time points. No patients received digestive decontamination or regional anesthesia during the 72 h prior to ICU admission.

3.5. Relationship between urinary 3-indoxyl sulfate and mortality

At 30 days after ICU admission, there was no detectable difference in mortality (18% low versus 5% high, $p = 0.07$). Low urinary 3-IS levels at 72 h after admission was associated with a statistically significant increase in mortality at one year (36% mortality for low 3-IS versus 9% for high, $p < 0.01$). Patients with low 3-IS levels had 22.5 ICU free days compared to 26 ICU free days in patients with high 3-IS levels ($p = 0.03$). The median value of urinary 3-IS at ICU admission was 17.2 among those who survived one year and was 7.5 among those who died ($p = 0.09$). The median value of urinary 3-IS after 72 h was 18.5 among those who survived one year and 2.06 among those who did not ($p < 0.01$). This is shown as a violin plot in Fig. 3. Examining median within-individual change in 3-IS, there was a decrease among those who died during follow-up but not among those who survived, although this was not statistically significant (0.63 IQR [0.24–1.63] for those who died versus 1.03 IQR [0.52–1.46] for those who survived, $p = 0.27$). Kaplan-Meier curves show the survival estimates between low and high urinary 3-IS at both follow-up times of 30 days (Fig. 4A) and one year (Fig. 4B). Since indole metabolism involves the liver [18] and indoxyl-sulfate is secreted by the kidneys [19], the disruption of these organs has the potential to affect urinary 3-IS levels. Therefore, we re-ran the primary analysis excluding those with the highest SOFA categories of both bilirubin and creatinine, and found similar associations with mortality (33% mortality for low 3-IS versus 6% for high 3-IS; $p < 0.01$). After adjusting for the presence of sepsis and the SOFA score in a multivariable model, low urinary 3-IS did not remain statistically significant with mortality (adjusted odds ratio for low 3-IS 2.81, 95% CI 0.61–12.9). This finding was substantively unchanged after stratifying for sex and for sepsis as the admitting diagnosis. A receiver-operator curve comparing SOFA score and urinary 3-IS levels at 72 h showed similar predictability of one-year survival with similar areas under the curves (Fig. 5). The number of culture-proven infections or patients with colonization of MDR organisms was not different between those with high versus low urinary 3-IS levels.

4. Discussion

In this prospective study, low levels of urinary 3-IS measured at 72 h after ICU admission was associated with a trend towards increased 30-day mortality and with significantly increased mortality within the year. This was true despite relatively small sample size and limited ability to

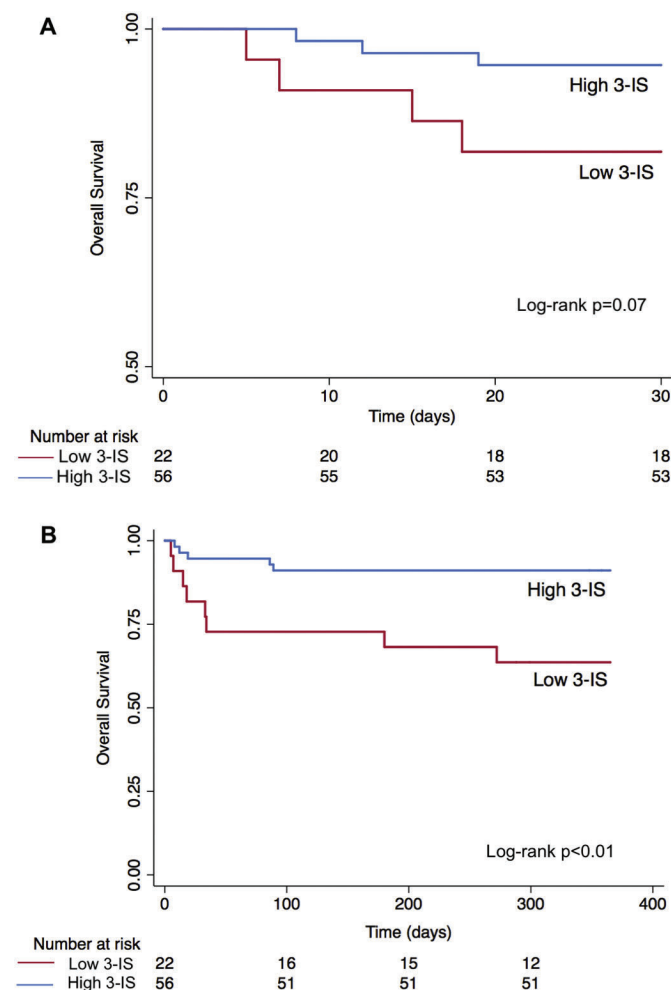


Fig. 4. Kaplan-Meier survival estimates. Kaplan-Meier curves show that low urinary 3-IS levels at 72 h after ICU admission have a trend towards increased mortality at 30 days (A) and significantly increased mortality at one year (B).

detect anything other than large differences in mortality. Levels of urinary 3-IS measured at ICU admission did not correlate with mortality at 30 days or one year after ICU admission. Those that died had a median decrease in urinary 3-IS levels, suggesting that the dynamics of urinary 3-IS may be more relevant to mortality in this cohort than the value ascertained immediately at the time of ICU admission. Urinary 3-IS at 72 h was a reasonably good predictor of mortality at one year compared to the well-established SOFA score.

Further studies will need to reexamine the relationship between urinary 3-IS and mortality at both the 30-day and one-year time points. An intact microbiome may confer long-term protection against poor clinical outcomes by providing colonization resistance and preventing infections weeks or even months after ICU discharge. On the other hand, the association between 3-IS and long term mortality suggests that 3-IS may represent baseline patient factors, such as frailty, but this study was not designed to assess frailty measures.

Disruption of the gut microbiome has been connected to critical illness as both a consequence and as a central driver of sepsis and multi-organ dysfunction [4,20]. There are clinical studies investigating strategies to augment the microbiome in critical illness with probiotics, prebiotics, synbiotics, or even fecal transplant, but none of these interventions have proven benefit [4,21]. Currently, the typical sequencing approach used to determine microbiome diversity is not rapid enough to determine in real time whether patients are good candidates for microbiome-based therapies. The ability to quickly assess and then

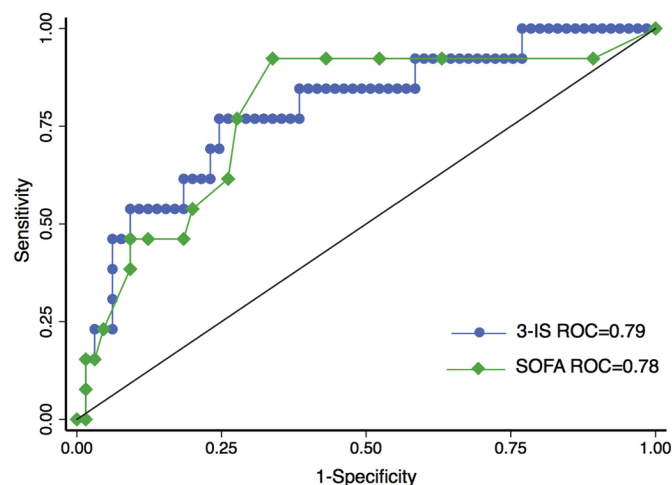


Fig. 5. Receiver-operator curves. The area under the curve of urinary 3-IS levels and SOFA scores after 72 h as predictors of survival at one year.

reassess microbiome “health” may be especially important in the ICU population as critically ill patients undergo rapid changes to their microbiome [1]. Based on the findings of our study and future studies needed to confirm our results, we hope that measuring urinary 3-IS will be useful as a risk assessment biomarker [22]. Furthermore, for clinical studies to be successful, it would be critical to have a marker that can rapidly identify patients that are at high risk for gut dysbiosis and then triage these patients into future studies aimed at modifying the microbiome.

Weber et al. first developed and studied urinary 3-IS as a marker for gut microbiota disruption in patients undergoing bone marrow transplant. They showed that low levels of urinary 3-IS within the first 10 days after bone marrow transplant was associated with higher transplant-related mortality and, similar to our study, low urinary 3-IS was also associated with worse overall one-year survival [11]. In contrast to our study, they showed that high urinary 3-IS was associated with Lachnospiraceae and Ruminococcaceae of the Clostridia class, and low levels of urinary 3-IS were associated with the Bacilli class [11]. Similarly to our study, they showed only a moderate correlation to alpha diversity ($r = 0.25$ with the Simpson Index). Tryptophanase is common and 3-IS and its metabolites are associated with a wide array of microbes [9]. Prior 3-IS studies have shown that prolonged use of systemic antibiotic treatment was associated with lower urinary 3-IS levels [11,23], which was not demonstrated in this ICU cohort, where immunosuppression was the only intervention that was associated with significant change of urinary 3-IS levels. This may reflect receipt of antibiotics in the recent past among our patients, before collection of the baseline sample.

A variety of biomarkers in sepsis and critical care have been evaluated, including cytokines, cell markers, vascular endothelial damage markers, and acute phase reactants, but none of them have been sensitive or specific enough to become routinely used in clinical practice [24,25]. The most widely studied marker is probably procalcitonin, which has been shown to be associated with ICU mortality in multiple studies [26,27] with an AUC ranging from 0.67 to 0.71 [28], which is comparable to the AUC of urinary 3-IS shown in our study. Despite this association, procalcitonin was unable to successfully guide the escalation of diagnostic and therapeutic management of sepsis in a large randomized controlled trial [29]. The difficulty in finding effective biomarkers for sepsis and critical illness may be due to the complex pathophysiology of sepsis and the inherent heterogeneity of ICU patients. Therefore, a combination of organ-specific markers or those used to guide therapies, such as the use of procalcitonin-guided antibiotic de-escalation [30,31], may be

where biomarkers eventually serve a larger role in clinical practice. There are a few biomarkers specific to the gut, such as serum citrulline and intestinal fatty acid-binding protein, which have both been independently associated with mortality in critically ill patients [32]. However, these are markers of enterocyte damage and, unlike urine 3-IS, would be unlikely to indicate if a patient would benefit from microbiome-directed interventions.

There are some strengths to our study. To our knowledge, this is the first study to investigate a potential biomarker specific to the microbiome in an ICU population, which includes a broad spectrum of illness types and severities. It included a detailed overview of patient characteristics associated with low urinary 3-IS levels and compared 3-IS to the well-established SOFA score. This study also has several limitations that are recognized. If urinary 3-IS is to be used as a marker to triage patients into future studies, ideally the initial level at admission could be used, but our study showed that only 3-IS level at 72 h was related to mortality. Similarly to procalcitonin, it may be the kinetics of urinary 3-IS that best guides management and timing of microbiome interventions in the ICU. Admission urine samples were not available for all patients in the study. Last, although this study included a variety of ICUs, it was relatively small and should be reproduced to confirm generalizability [33].

5. Conclusions

In summary, we found that low levels of urinary 3-indoxyl sulfate at 72 h after ICU admission was associated with a fewer ICU-free days and with one-year but not 30-day mortality. Future, larger studies should test whether urinary 3-IS can identify ICU patients that will benefit from targeted microbiome interventions.

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Author contributions

SZK: data curation, investigation, formal analysis, writing manuscript. KD: data curation, investigation. MKA: data curation, formal analysis, reviewing manuscript. DHC: reviewing manuscript. ACU: formal analysis, reviewing manuscript. JAA: reviewing manuscript. PJO: reviewing manuscript, data curation. DEF: conceptualization, formal analysis, supervision, reviewing manuscript.

Declaration of Competing Interest

None.

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Original Article

Evolution of the environmental microbiota of a new neonatal intensive care unit (NICU) and implications for infection prevention and control

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Abstract

Objective: To describe changes in the environmental microbiota of a new neonatal intensive care unit (NICU) and potential implications for infection prevention and control (IPC) efforts.

Design: Prospective observational study.

Setting: A newly constructed level IV neonatal cardiac intensive care unit (NCICU) before and after patient introduction and the original NICU prior to patient transfer.

Methods: Environmental samples were obtained from the original NICU prior to patient transfer to a new NCICU. Serial sampling of patient rooms and provider areas of the new NICU was conducted immediately prior to patient introduction and over an 11-month study period. Microbiota at each sampling point were characterized using Illumina sequencing of the V3/V4 region of the 16S rRNA gene. Microbiota characteristics (α and β diversity and differential abundance) were compared based on time, location, and clinical factors (room-level antibiotic use and patient turnover).

Results: An immediate increase in the environmental differential abundance of gut anaerobes were seen after patient introduction. There was an increase in the relative abundance of *Staphylococcus* spp, *Klebsiella* spp, *Pseudomonas* spp, and *Streptococcus* spp over time. The new NCICU consistently showed more diverse microbiota and remained distinct from the original NICU. The microbiota of the provider areas of the NCICU eventually formed a cluster separate from the patient rooms. Patient turnover increased room-level microbiota diversity.

Conclusion: Microbiota characteristics of the new NICU were distinct from the original ICU despite housing similar patients. Patient and provider areas developed distinct microbiota profiles. Non-culture-based methods may be a useful adjunct to current IPC practice.

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Studies from established neonatal intensive care units (NICUs) demonstrate diverse microbiota in the built environment that surrounds neonates.¹ Exchange of organisms between the microbiota of the built environment and resident neonates has been described,² and neonates in different locations within the same hospital are colonized with location-specific microbiota profiles.³ The NICU microbial environment thus plays a role in the development of hospitalized infants' microbiota⁴ and could moderate acquisition of pathogenic organisms. However, the initial microbiota of the built environment of the NICU before patient introduction and its evolution over time after patient introduction have not been well described.⁵

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Insights as to how patient introduction may shape the built environment of hospital units have previously come from the hospital setting caring for adults.^{6,7} For example, in a large tertiary-care adult hospital, the introduction of patients was associated with an increase in skin-associated genera (eg, *Corynebacterium*, *Staphylococcus*, and *Streptococcus*, with concurrent decreases in the abundance of *Acinetobacter* and *Pseudomonas*), which had dominated samples prior to opening.⁸ Describing the built environment of a NICU prior to introducing patients, and its evolution over time would help better delineate the NICU built environment–neonate interaction and could potentially help assess the effectiveness of routine infection prevention and control (IPC) practices in controlling colonization in the built environment over time.

In this study, we used the opening of a new neonatal cardiac intensive care unit, (NCICU) to describe the microbiota of the built

environment prior to admitting patients and periodically after patient introduction. We compared microbial community changes over time within the new NCICU and between the new NCICU and the microbiota of the built environment of the previous NICU within the same hospital, which housed the same patients prior to transfer. We hypothesized that (1) the built-environment microbiota of the new NCICU would gradually become similar to that of the built environment of the previous NICU location and (2) that specific clinical variables such as antibiotic use and patient turnover would have a measurable impact on the microbiota of the built environment in the new NCICU.

Methods

Study design

This was an 11-month prospective longitudinal study carried out at NewYork-Presbyterian Morgan Stanley Children's Hospital, a 200-bed academically affiliated tertiary-care hospital. Two geographically separate locations in the same hospital were included in built-environment surveillance: the original 50-bed NICU, and a newly constructed 17-bed NCICU. On September 27, 2017, the existing NICU transferred some patients to the new NCICU. The Columbia University Irving Medical Center Institutional Review Board approved this study with a waiver of informed consent.

Environmental sampling strategy

Samples from the built environment were collected from 7 patient rooms in the original NICU housing cardiac patients the day before infants were transferred to the new NCICU. On the same day, samples were collected from 5 empty patient rooms and 1 common staff area in the new NCICU; simulations had been performed in the new NCICU during the weeks prior to patient transfer. Samples from these same locations were then collected from the new NCICU over an 11-month period, approximately doubling the time interval between each sample collection: new NCICU days 1, 5, 9, 16, 33, 61, 89, and 304. This sampling frequency was adopted to be more sensitive to early shifts in the built-environment microbiota while reducing the burden of sample collection and analysis.

Built environment sampling procedure

Specific surfaces were targeted for sampling in each patient room in both the original and the new units. These surfaces were determined a priori in collaboration with IPC personnel based on past outbreak investigations and surveillance efforts because they were the most commonly contaminated, as determined by bacterial cultures. Surfaces within a room were swabbed using a single, large, sponge-type swab (3M Product ID no. 70200750951). This technique, which combined multiple surfaces, was done to increase total microbial content gathered from each room and to improve the signal-to-noise ratio within each sample.² In each room, each surface was swabbed for 2–3 minutes each in the following order: bedrails and surfaces of isolettes, monitors, and infusion pump high-touch surfaces, inside door handles, and diaper scales. This order was selected so that the surfaces closest to the baby were swabbed first, successively moving to surfaces that were likely to have greater bacterial density. We also collected swabs from the common provider workplace area where the surfaces included countertops, computer mouse and keyboard, and chair armrests.

Sample processing and cultures

After collection, swabs were squeezed and drained for 1 minute to yield 2.5 mL of fluid. Aerobic cultures were also performed for (1) vancomycin-resistant *Enterococcus* (VRE), (2) methicillin-resistant *Staphylococcus aureus* (MRSA) (Remel), and (3) multidrug-resistant gram-negative rods using Chromagar. These samples were then stored frozen at -80°C for batched DNA extraction and subsequent 16S rRNA sequencing of microbial DNA.

Infection prevention and antibiotic practices in the new NCICU

According to prior established IPC policy, routine cleaning and disinfection of the NCICU was performed twice daily using disposable wipes and a bleach-based product throughout the study period. Environmental surfaces and points of patient or healthcare worker contact were targeted during daily cleaning. Upon patient discharge or transfer between locations, an additional terminal cleaning was performed, which included removal of curtains, remaining supplies, ventilators, and any residual patient care equipment. The neonatal isolettes are exchanged every 14 days and are cleaned at a dedicated equipment center. Empiric antibiotic use protocols and hand hygiene compliance in both the NICU and NCICU were reviewed for differences and were noted if present.

Sequencing and microbiota analysis

DNA was extracted using the Qiagen AllPrep PowerViral DNA/RNA Kit. The V3/V4 region of the 16S rRNA gene was amplified using established primers⁹ with Illumina Nextera adaptors. Libraries were multiplexed using Illumina Nextera XT Index kits and were normalized and pooled with 10% PhiX. Sequencing was performed on an Illumina MiSeq platform (MiSeq Reagent kit v3, 600 cycles). 16S rRNA sequences were processed using QIIME for quality-filtering, trimming, dereplication, and chimeric sequence filtering of FASTQ sequences through the National Institute of Allergy and Infectious Diseases Nephel platform.¹⁰ In total, 61 samples were sequenced, and 60 of these samples passed the minimum read cutoff of 7,500 reads for inclusion in further analysis. Low-abundance operational taxonomic units (OTUs) with relative abundance $<0.005\%$ were filtered out using the R package phyloseq v1.28.0.¹¹ Clustering of filtered reads into OTUs at 97% similarity was performed. The Greengenes 97% database was used as a reference database for taxonomic classification of these OTUs.¹²

Relative abundances of specific taxa were calculated and compared between the original and new units, as well as across time in the new unit. The pipeline used in this study, DESeq2, uses a generalized linear model to analyze log 2 fold changes in differential abundance. The Wald test was used for significance testing with adjustment for multiple testing using the Benjamini and Hochberg test.¹³ Principal coordinate analysis of weighted UniFrac β diversity was used to assess overall similarity between samples collected based on (1) the date of collection and (2) the geographical location of the samples within the NCICU.

The Chao index was used to quantify α diversity, which was compared between the original and the new NICUs. We determined the correlation of changes in room-specific α diversity between sampling time points and 2 room-level clinical exposures of interest: (1) interval broad-spectrum antibiotic use, and (2) interval patient turnover using samples obtained during the last



First, even prior to the introduction of patients, diverse microbiota including taxa of clinical importance were detected in the built environment. The initial microbiota profile was disrupted almost immediately with patient introduction. The most noticeable change with patient introduction was an increase in anaerobic organisms which have been associated with the neonatal gut.¹⁴ While not unexpected, the immediacy of the change was striking.

The built-environment microbial communities from locations in the original NICU remained distinct from locations in the new NCICU at all study time points (Fig. 3). The microbiota of the previous NICU location just prior to patient transfer was characterized by an abundance of *Pseudomonas* OTUs. The common staff areas in the new NCICU were initially closer to the microbiota profiles of patient rooms, but over time these microbiota profiles diverged toward a distant distinct cluster that aligned closer with that of the original NICU; both were dominated by *Pseudomonas* (Fig. 3).

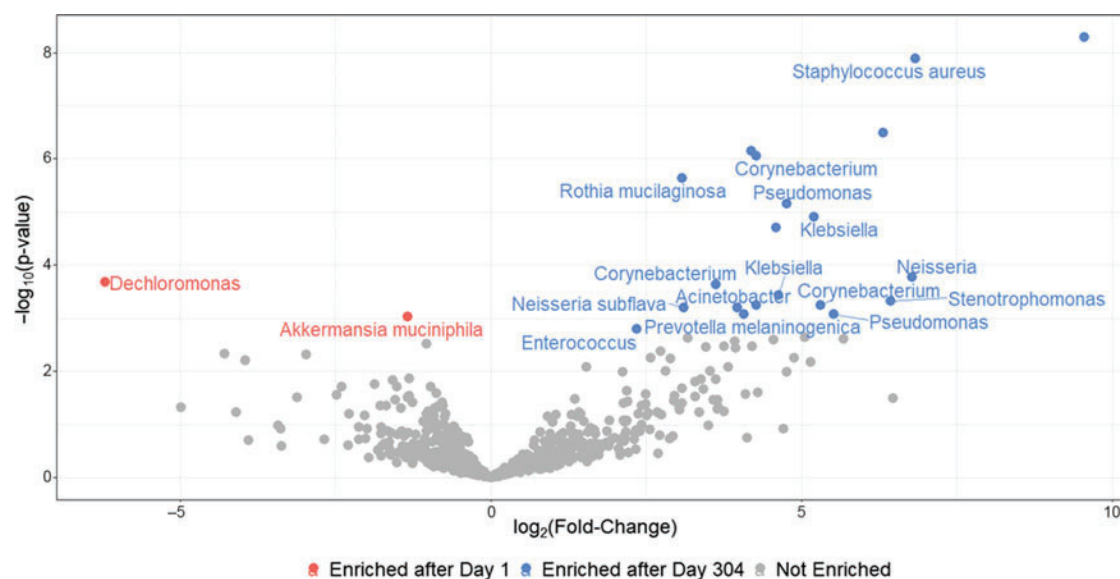


Fig. 2. Volcano plot demonstrating changes in relative taxon abundance between baseline and at end of study period.

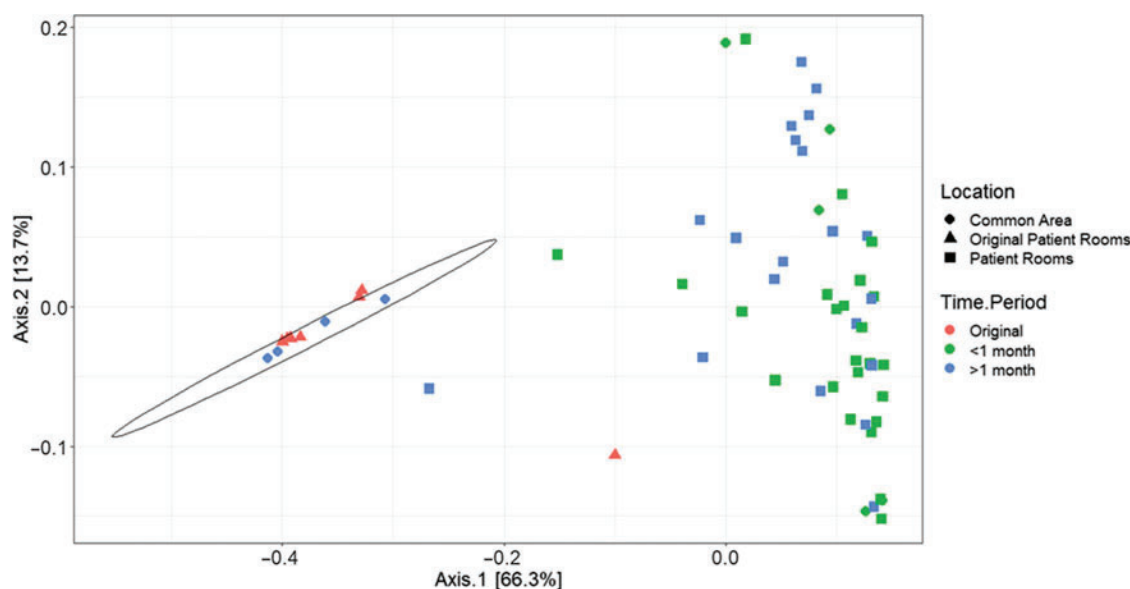


Fig. 3. The β diversity plots demonstrating clustering of samples across time and location. In the later period, samples collected from the common area cluster together with samples from the original NICU. The circle is an ellipse assuming multivariate t distribution drawn around the samples from the common area over 1 month after patient introduction.

and implies that patients' impact on the environment could outpace routine IPC interventions. Over time, after patient introduction, clinically relevant organisms, such as *Enterobacteriaceae*, *Pseudomonas*, and *Staphylococcus*, occupied a larger fraction of the microbiota of the built environment of patient rooms. This gradual increase occurred despite IPC activities designed to mitigate patient-to-environment transfer: daily cleaning, terminal cleaning, and barrier precautions for patients with MDROs. The scope of these changes were not identified using routine surveillance and indicate the potential benefit of molecular methods in identifying rapid changes in a local environment prior to being reflected in clinical or environmental cultures.

The dominance of the ICU built environment with these hospital-specific organisms has been demonstrated previously.¹⁵ Possible explanations for this preferential organism burden include the cumulative pressure of local antibiotic use, organism propensity to create biofilms resistant to regular cleaning practices,¹⁶ or a continued reservoir of organisms contributed by healthcare providers. Across all time points, however, the built environment of the NCICU remained distinct from the original location. The original NICU was characterized by a low-diversity state seen in established ICU-type settings.¹⁷ Our findings thus illustrate the difference that altering the physical location makes to the microbiota of the patient environment within the same

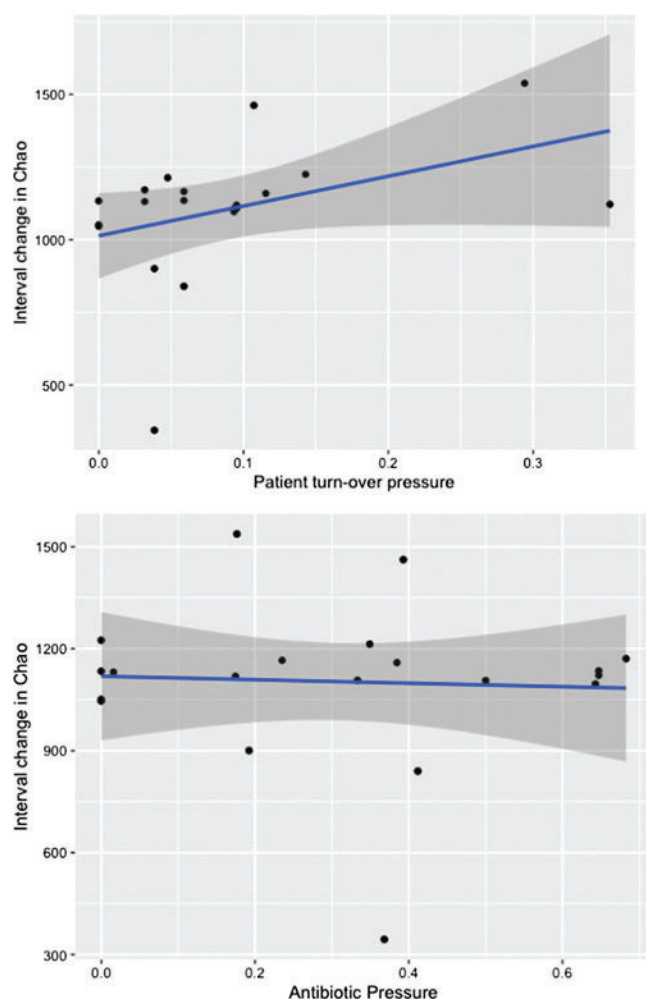


Fig. 4. Changes in α diversity (Chao index) against interval number of occupants and interval antibiotic use. Both variables were normalized for interval days.

hospital, at least in the short term, which is consistent with previous work.³

The microbiota of the common area of the NCICU, frequented by providers, initially resembled patient areas. However, the common area eventually formed a separate cluster. This dissimilarity between patient and provider areas is a desirable outcome from an infection control perspective, indicating limited transfer of organisms from patient rooms to shared areas. Distinct microbiota niches within the hospital environment have been described in adult settings^{6,8} Correlating these separate profiles with relevant IPC practice could help monitor compliance.

Interestingly, microbiota profiles of common staff areas of the new NCICU quickly became similar to those of the original NICU with a high dominance of *Pseudomonas*. Some providers staff both units, which could contribute to this finding. Whether provider work stations act as reservoirs for typical hospital associated pathogens across hospital units either because of traffic, suboptimal cleaning, or proximity to *Pseudomonas* reservoirs (eg, sinks) should be further studied. This finding also illustrates the application of these techniques to identify routes of transmission between areas based on similarity between microbiota profiles.

The microbiota in the rooms in the new NICU remained mostly similar over time. The impact of modifiable factors, such as antibiotic use on the microbiota, was limited. The limited impact of

antibiotic use observed could be because of the relatively short study duration, long hospital stays, and relatively low rates of broad-spectrum antibiotic use compared to adult units.¹⁸ In contrast, a positive association with increased diversity was observed with patient turnover, suggesting that influx of new patients and interval terminal cleanings may help reset microbial diversity.

This study has several limitations. The sample size was small, and our patient population was restricted to neonates with complex cardiac issues, which limits the generalizability of our findings. Species-level identification was not available for all taxa, so the attribution of potential clinical significance may not be fully accurate. Routine cultures were mostly negative, so viability of organisms could not be ascertained. Multidrug-resistant organisms were not isolated in the environment, which may limit generalizability. The lack of identification of antibiotic resistance using molecular methods limits inference around the impact of antibiotic use. This study was limited by a lack of a quantitative measure of bioburden. Due to our swabbing technique, we were unable to distinguish between surfaces sampled within each room. Also, we did not sample patients or healthcare workers which limits inference about transmission.

In summary, the introduction of patients into the hospital environment, leads to time-dependent and clinical care-dependent changes in the resident microbiota. Patient turnover may influence the overall structure of the microbiota in the built environment. Non-culture-based methods to track environmental microbiota may reveal patterns of transmission and colonization missed by regular cultures and may be a useful adjunct to current IPC practice.

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Conflicts of interest. All authors report no conflicts of interest relevant to this article.

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Prevalence and Risk Factors for Inappropriate Continuation of Proton Pump Inhibitors After Discharge From the Intensive Care Unit

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Abstract

Objective: To determine the prevalence and risk factors for inappropriate discharge on proton pump inhibitor (PPI) therapy started in the intensive care unit (ICU) for stress ulcer prophylaxis.

Patients and Methods: This was a retrospective cohort study of adults initiated on treatment with a PPI in any of 9 affiliated ICUs from January 1, 2014, to December 31, 2018. Patients were excluded if they had an appropriate long-term PPI indication. Logistic regression modeling was used to identify characteristics associated with discharge on treatment with an inappropriate PPI.

Results: Of 24,751 patients admitted to an ICU, 4127 were initiated on treatment with a new PPI, with 2467 (60%) lacking a long-term PPI indication. Of these 2467, a total of 1122 (45%) were continued on PPI therapy after transfer to the floor and 668 (27%) were discharged on PPI therapy. On multivariable analysis, risk factors for inappropriate discharge on PPI therapy included having an upper endoscopy (adjusted odds ratio [aOR], 1.70; 95% CI, 1.08-2.66), admission to the surgical compared with medical ICU (aOR, 2.03; 95% CI, 1.32-3.10), and discharge to a nursing home or rehabilitation facility (aOR, 1.43; 95% CI, 1.04-1.96; and aOR, 2.29; 95% CI, 1.62-3.24, respectively).

Conclusion: Among patients started on treatment with a PPI in the ICU without an indication for outpatient PPI use, 27% (668 of 2467) were nonetheless discharged on PPI therapy. Medically complex and surgical ICU patients are at increased risk for receiving PPIs without appropriate documented indications, and careful review of medication lists at discharge should occur in these high-risk groups.

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Proton pump inhibitors (PPIs) are one of the most commonly prescribed medications in the world, and their use has increased substantially in recent years.^{1,2} Although they are highly effective and safe when used for appropriate indications, they are also one of the most frequently overused medications.³⁻⁵ Prior studies have suggested that 60% to 80% of PPI therapy started in the hospital lacks an appropriate long-term indication.⁶⁻⁸ Despite earlier concerns about long-term adverse consequences of PPI use, the overall safety profile of PPIs is probably favorable.⁹⁻¹⁶ Still, it is wasteful to continue them in the outpatient setting unless they have some reasonable probability of benefit.¹⁷⁻²¹ For this reason, PPIs have been a

common target of initiatives aimed at reducing low-value care.²²⁻²⁵

Stress ulcer prophylaxis with short-term PPI therapy is common in the intensive care unit (ICU). Clinically important gastrointestinal (GI) bleeding occurs in approximately 2% to 3% of ICU patients, with as many as 70% of ICU patients receiving some form of acid suppression in prior studies.^{26,27} Guidelines vary but typically recommend acid suppression with PPIs or histamine 2 receptor antagonists for ICU patients with coagulopathy, prolonged mechanical ventilation, history of upper GI bleeding, traumatic brain injury or burn injury, severe sepsis, or use of steroids or antiplatelet medications.^{28,29}



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Prior studies have suggested that PPIs prescribed during hospitalization are frequently continued after hospitalization without indication,^{17,30,31} including 3 small studies of ICU patients in which most patients were continued on PPI therapy at discharge after transfer from the ICU.^{32,33} However, there are no studies identifying which ICU patients are most at risk for being inappropriately continued on PPI therapy at discharge. We sought to estimate the prevalence of this problem among ICU patients at our institution and also to identify predictors of inappropriate PPI therapy continuation.

PATIENTS AND METHODS

Population

This was a retrospective cohort study of patients 18 years or older who were admitted to 1 of the 9 ICUs at Columbia University Medical Center between January 1, 2014, and December 31, 2018, and survived to discharge. For patients who were admitted multiple times during the period, only the first hospitalization was included. During each patient's hospitalization, medication reconciliation notes documenting the medications at admission, transfer, and discharge were electronically parsed for use of PPIs. Patients were included in the study if they received a PPI while in the ICU and had not been on PPI therapy earlier in the hospitalization or before admission, as determined by the medication reconciliation notes. Patients were then excluded from the primary analysis if they had a documented indication for long-term PPI use based on clinical notes from the same time points. Indications for PPI use included ulcers, esophagitis, or erosions on upper endoscopy; diagnostic codes for gastroesophageal reflux disease, Barrett esophagus, peptic ulcer disease, or *Helicobacter pylori* infection; having received a lung transplant; or discharge on treatment with nonsteroidal anti-inflammatory drugs, dual antiplatelet therapy, or an antiplatelet medication with an anticoagulant (Supplemental Table 1, available online at <http://www.mayoclinicproceedings.org>). This left 2467

patients (60% of the 4127 initiated on PPI therapy in the ICU) who lacked a documented long-term indication and made up the primary analysis population.

Exposures

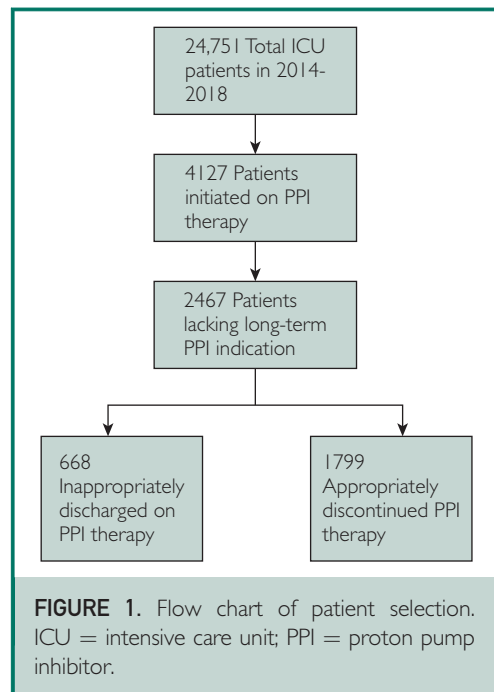
Demographic, hospitalization, and medical covariates were extracted from the electronic medical record using automated queries. These covariates included age, sex, race, ICU type, admission service, discharge destination, length of stay, number of discharge medications, ventilation requirement during admission, Charlson Comorbidity Index score calculated from *International Classification of Diseases* (versions 9 and 10) codes, and upper endoscopy findings. Continuous variables such as length of stay and number of discharge medications were converted to categorical variables by dividing the data into equal tertiles.

Primary Outcome

The primary outcome was inappropriate continuation of PPI therapy at the time of hospital discharge. This was classified based on the discharge medication reconciliation note, which must be completed before discharge in all patients (ie, there is a computerized "hard stop" preventing finalization of the electronic discharge order unless the medication reconciliation is performed and documented). A secondary outcome was inappropriate continuation of PPI therapy at the first primary care follow-up visit among patients who had primary care visits available to review in our health care system. Again, PPI assertion was through the electronic medication reconciliation that must be performed before finalizing this outpatient visit.

Statistical Approach

Categorical variables were compared using χ^2 tests, and continuous variables were compared using Student *t* test or Wilcoxon rank sum test for non-normally distributed data. A multivariable logistic regression model was developed to determine covariates significantly associated with discharge on PPI therapy among patients with no



long-term PPI indication who were initiated on PPI therapy in the ICU. Potential predictors were identified based on clinical expertise as those most likely to be associated with inappropriate PPI therapy continuation post-ICU. The initial model was developed by including the predictors that were significant at alpha level of .20 on univariable analysis. To determine variables that were retained in the final reduced model, we manually removed nonsignificant variables 1 by 1 beginning with those believed to be the least important clinically. Variables in the final model all had a significant independent relationship with the outcome at the .05 level.

Statistical analysis was performed using Stata (StataCorp, version 16), with alpha level of .05 unless otherwise stated. The Columbia University Institutional Review Board approved this study.

RESULTS

Population

There were 24,751 patients admitted to one of the 9 adult ICUs at 2 affiliated hospitals in 2014 to 2018 who survived to discharge

(Figure 1). These included 3 medical ICUs (n=5300; 21%), 2 cardiac ICUs (n=4885; 20%), 2 cardiothoracic ICUs (n=6585; 27%), 1 surgical ICU (n=3266; 13%), and 1 neurological ICU (n=4715; 19%). Of these 24,751 patients, 4127 (17%) were initiated on PPI therapy while in the ICU (had not received a PPI earlier in the hospitalization and no PPI was listed on the admission medication reconciliation).

Of the 4127 patients initiated on PPI therapy in the ICU, 2467 (60%) lacked documentation of a long-term indication and were therefore presumed to be for short-term use, such as stress ulcer prophylaxis. Further, 1122 of these patients (45% of those lacking an indication, 27% of all PPI therapy initiated in ICU) were continued on the PPI therapy at transfer to the floor. Finally, 668 (27% of those lacking an indication, 16% of all PPIs initiated in ICU) were ultimately discharged on PPI therapy without a long-term indication (Figure 2). Of the patients discharged on unnecessary PPI therapy who had primary care records available, 18 of 28 (64%) were continued on the PPI therapy at their follow-up appointment without documentation of an indication for its prescription.

Patient Characteristics

On univariable analysis, compared with patients whose PPI therapy was appropriately discontinued, patients inappropriately continued on PPI therapy were more likely to be women, be discharged from the neurosurgery service, have a higher number of providers during their hospitalization, have undergone upper endoscopy, have a longer length of stay and more discharge medications, and be discharged to a skilled nursing or rehabilitation facility (Table 1). Patients discharged on inappropriate PPI therapy were less likely to have been intubated during admission. On univariable analysis, patients inappropriately discharged on PPI therapy had a higher mean Charlson Comorbidity Index score at 4.03 compared with 3.66 in patients whose PPI was appropriately discontinued ($P=.001$).

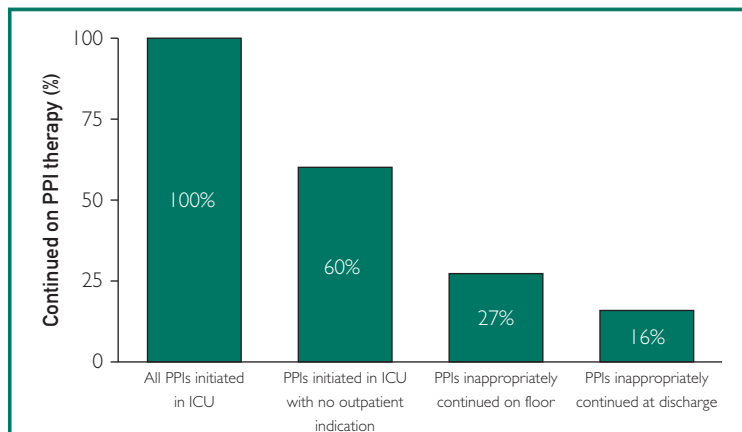


FIGURE 2. Cumulative rates of proton pump inhibitor (PPI) therapy continuation at care transition points. Of 24,751 intensive care unit (ICU) patients, 4127 were initiated on PPI therapy (450 in the medical ICU, 693 in the cardiac ICU, 582 in the surgical ICU, 1765 in the cardiothoracic ICU, and 637 in the neurological ICU). Of PPI therapy initiated in the ICU, 60% lacked a long-term indication and 16% of these were inappropriately continued at discharge.

Upper Endoscopy

There was a significant association between undergoing upper endoscopy during hospitalization and discharge on PPI therapy, even after excluding patients with findings that would warrant acid suppression. There were 288 patients initiated on PPI therapy in the ICU who underwent upper endoscopy during admission (28% [n=82] for melena, 15% [n=42] for hematemesis, 4% [n=12] for coffee ground emesis, 7% [n=19] for hematochezia, 8% [n=24] for anemia or heme-positive stool, 9% [n=25] for endoscopic retrograde cholangiopancreatography, 11% [n=31] for percutaneous endoscopic gastrostomy tube placement, 6% [n=16] for dysphagia, and the remaining 13% [n=37] for other reasons, including abnormal imaging results, varices screening, vomiting, or abdominal pain).

Of these 288 patients, 115 had normal endoscopy findings. Of these, 59 (51%) were still discharged on PPI therapy compared with 137 of 173 (79%) patients with abnormal findings ($P<.001$). Among the 137 patients with abnormal findings were 8 patients who had blood or clot seen during endoscopy without an observed underlying lesion. These were considered

potentially obscuring lesions that would warrant acid suppression, and continuation on PPI therapy for these patients was considered appropriate. Of the 4 of those who did not have an additional reason for acid suppression, none were discharged on PPI therapy. After excluding patients with PPI indications (such as gastroesophageal reflux disease, ulcers, esophagitis, *H pylori* infection, or erosions on endoscopy), there were 98 patients who underwent upper endoscopy, with 83 of these having normal findings. Of these, 39 of 83 (47%) were still discharged on PPI therapy compared with 8 of 15 (53%) of those who had abnormal findings on endoscopy that would not necessarily warrant PPI prescription, such as arteriovenous malformations, masses, and varices ($P=.65$).

Mechanical Ventilation

Of the 2467 patients without a long-term PPI indication, 1715 (70%) were mechanically ventilated during admission, and 781 (32%) were ventilated for more than 48 hours. Mechanical ventilation overall was associated with a reduced likelihood of discharge on PPI therapy (in 23% [386 of 1715] of ventilated patients vs 38% [282 of 752] of never ventilated patients; $P<.001$), but there was no significant difference in rates of PPI therapy continuation at discharge in those ventilated for more than 48 hours vs those who were not (29% [224 of 781] vs 26% [444 of 1686], respectively; $P=.22$).

ICU Type

There were substantial differences in the rates at which ICUs of different types started and managed PPI therapy (Table 2). The cardiothoracic ICUs (CTICUs) had the highest proportion of patients initiated on new PPI therapy at 27% (1765 of 6588), while the medical ICUs had the lowest proportion at 8.5% (450 of 5300). However, most PPI therapy started in the CTICU (1465 of 1765; 83%) was only given in the ICU and not continued on the floor or at discharge. The surgical ICU and neurological ICU had the highest percentages of patients

INAPPROPRIATE PPI CONTINUATION AFTER ICU STAY

TABLE 1. Characteristics of Patients Started on PPI Therapy in the Intensive Care Unit Without Documented Long-term Indication

Table 1: Characteristics of Patients on Started on Proton Pump Inhibitors in the ion			
Characteristic	PPI Appropriately Discontinued (n=1799)	PPI Inappropriately Continued at Hospital Discharge (n=668)	P
Age tertile (y), no. (%)			
18-56	707 (39)	287 (43)	.23
56-70	609 (34)	207 (31)	
>70	483 (27)	174 (26)	
Sex, no. (%)			
Male	1081 (60)	363 (54)	.01
Female	718 (40)	305 (46)	
Race, no. (%)			
White	808 (45)	302 (45)	.77
Black	183 (10)	72 (11)	
Asian	73 (4)	32 (5)	
Other/unknown	735 (41)	262 (39)	
Admit service, no. (%)			
Medicine	540 (30)	216 (32)	<.001
Neurology	193 (11)	74 (11)	
Surgery	840 (47)	255 (38)	
Neurosurgery	153 (9)	108 (16)	
Other	73 (4)	15 (2)	
Charlson Comorbidity Index score, no. (%)			
0-2	652 (36)	198 (30)	.003
3-5	759 (42)	294 (44)	
>5	388 (22)	176 (26)	
Intubated during admission, no. (%)			
No	470 (26)	282 (42)	<.001
Yes	1329 (74)	386 (58)	
No. of providers, no. (%)			
1-11	718 (40)	211 (32)	<.001
12-18	638 (35)	225 (34)	
>18	443 (25)	232 (35)	
No. of hospital locations, no. (%)			
1-3	858 (48)	352 (53)	.06
4	434 (24)	155 (23)	
>4	507 (28)	161 (24)	
Length of hospital stay (d), no. (%)			
1-7	733 (41)	198 (30)	<.001
8-15	587 (33)	201 (30)	
>15	479 (27)	269 (40)	
Underwent upper endoscopy, no. (%)			
No	1748 (97)	621 (93)	<.001
Yes	51 (3)	47 (7)	
Discharge destination, no. (%)			
Home	732 (41)	186 (28)	<.001
Home with services	607 (34)	223 (33)	
Rehabilitation facility	147 (8)	115 (17)	
Skilled nursing facility	273 (15)	133 (20)	
Other/against medical advice	18 (1)	6 (1)	

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TABLE 1. Continued

Table 1: Characteristics of Patients on Started on Proton Pump Inhibitors in the ion			
Characteristic	PPI Appropriately Discontinued (n=1799)	PPI Inappropriately Continued at Hospital Discharge (n=668)	P
Discharge destination, no. (%), continued			
Hospice	22 (1)	5 (1)	
No. of discharge medications, no. (%)			
0-7	992 (55)	265 (40)	<.001
8-10	424 (24)	155 (23)	
>10	383 (21)	248 (37)	

PPI = proton pump inhibitor.

discharged on PPI therapy without an indication, at 6% (191 of 3266) and 4% (196 of 4715), respectively, among all patients admitted to an ICU during the period ($P<.001$).

Multivariable Logistic Regression Model

A multivariable logistic regression model was developed among all patients initiated on PPI therapy in the ICU who lacked a long-term indication for acid suppression (Table 3). The outcome was inappropriate continuation of PPI therapy compared with appropriate discontinuation of PPI therapy at hospital discharge. The predictors significantly associated with discharge on inappropriate PPI therapy in this model were admission to the surgical ICU relative to the medical ICU (adjusted odds ratio [aOR], 2.03; 95% CI, 1.32 to 3.10), discharge to a rehabilitation facility (aOR, 2.29; 95% CI, 1.62 to 3.24) or skilled nursing facility (aOR, 1.43; 95% CI, 1.04 to 1.96) relative to home, undergoing upper endoscopy (aOR, 1.70; 95% CI, 1.08 to 2.66), and increasing number of medications at discharge (aOR, 2.40 for >10 medications relative to <8 medications; 95% CI, 1.88 to 3.06). Predictors associated with decreased odds of discharge on inappropriate PPI therapy were intubation during hospitalization (aOR, 0.57; 95% CI, 0.44 to 0.73), an increasing number of physical locations (ie, more transfers) during hospitalization (aOR, 0.70 for >4 compared with <4 locations; 95% CI, 0.54 to 0.91), and admission

to the CTICU relative to the medical ICU (aOR, 0.33, 95% CI, 0.21 to 0.51). Although increasing Charlson Comorbidity Index score was significantly associated with discharge on an inappropriate PPI on univariable analysis ($P=.001$), it did not remain significantly associated with inappropriate discharge on PPI therapy on multivariable analysis.

Modified Poisson Regression Model

The primary analysis in this study was a multivariable logistic regression model, which provides an estimate of the odds ratio (OR) for inappropriate discharge on PPI therapy for the various predictors. Because the OR may overestimate the relative risk as the outcome of interest becomes more frequent, a sensitivity analysis was performed using a modified Poisson regression model with robust error variance to determine the relative risks of the exposures of interest.³⁴ These results did not substantively differ from the original logistic regression model. Though as expected, the adjusted relative risks for each predictor were somewhat lower than the aORs in the primary logistic regression model, all of the significant predictors remained significant in the sensitivity analysis (Supplemental Table 2, available online at <http://www.mayoclinicproceedings.org>).

DISCUSSION

Low-value medications are a common cause of waste in the modern health care system, with several campaigns such as the Choosing

TABLE 2. Percent of Patients From Each ICU Discharged on PPI Therapy

ICU type	Started on PPI in ICU, no. (%)	PPI Continued Inappropriately on Transfer to Hospital Floor, no. (%)	PPI Continued Inappropriately at Hospital Discharge, no. (%)	PPI Appropriately Discontinued at Hospital Discharge, no. (%)
Medical ICU (n=5300)	450 (9)	164 (3)	84 (2)	80 (2)
Cardiac ICU (n=4885)	693 (14)	166 (3)	99 (2)	67 (1)
Surgical ICU (n=3266)	582 (18)	268 (8)	191 (6)	77 (2)
Cardiothoracic ICU (n=6585)	1765 (27)	155 (2)	98 (2)	57 (1)
Neurological ICU (n=4715)	637 (14)	369 (8)	196 (4)	173 (4)

ICU = intensive care unit; PPI = proton pump inhibitor.

Wisely Initiation of the American Board of Internal Medicine aimed at reducing unnecessary drug prescriptions.^{35,36} Proton pump inhibitors are one of the most commonly overused medications in the United States, with most estimates suggesting that half the PPI prescriptions are medically unnecessary.^{6-8,37} New medications are frequently started during acute hospitalizations and then continued at discharge despite absence of a clear long-term indication.³⁸ Because PPIs are used in the acute setting for stress ulcer prophylaxis in the ICU, they often fall into this category. This study sought to measure the prevalence of discharge on an inappropriate PPI therapy among patients who first received one in the ICU and determine risk factors for inappropriate discharge on long-term PPI therapy after hospitalization in the ICU. We found that among ICU patients started on PPI therapy without a long-term indication, 45% (1122 of 2467) were continued on the PPI therapy on the floor and 27% (668 of 2467) were ultimately discharged on treatment with the PPI.

Three prior small studies were identified that sought to estimate the prevalence of inappropriate continuation of acid suppression started during an ICU admission.^{32,33,39} These 3 studies included a total of 849 patients in 4 medical and surgical ICUs and

found rates of inappropriate PPI therapy continuation at the time of hospital discharge from 24% to 39%. In a study of 248 patients who were started on acid suppression in the surgical ICU, Murphy et al³⁹ found that patients with longer hospitalizations and more risk factors for GI bleeding were more often continued on acid suppression therapy, but that only 5% of patients continued on acid suppression therapy had a compelling reason for it at discharge. Unlike these prior studies, this study focused on predictors of inappropriate PPI therapy continuation, including differences in PPI prescribing patterns based on ICU type. A total of 9 ICUs were involved in this study, including medical, surgical, neurological, and cardiac ICUs. We found that the medical ICU started the lowest proportion of its patients on PPI therapy at 9% (450 of 5300) compared with 28% (1765 of 6585) of patients in the CTICU and 18% (582 of 3266) of patients in the surgical ICU (Table 2). However, most PPI therapy initiated in the CTICU was stopped before transfer to the floor. Only 2% (155 of 6585) of CTICU patients were transferred to the floor with an inappropriate PPI therapy compared with 8% (268 of 3266) of surgical ICU patients and 3% (164 of 5300) of medical ICU patients. Patients in the CTICU

TABLE 3. Multivariable Model of Predictors of Discharge on PPI Therapy Among Patients Initiated on PPI in the ICU Without Long-term Indication

Characteristic	Adjusted Odds Ratio (95% CI)	P
ICU where PPI started		
Medical ICU	1 (reference)	
Cardiac ICU	1.31 (0.90-1.92)	.16
Surgical ICU	2.03 (1.32-3.10)	.001
Cardiothoracic ICU	0.33 (0.21-0.51)	<.001
Neurological ICU	1.49 (0.79-2.83)	.22
Discharge destination		
Home	1 (reference)	
Home with services	1.27 (0.98-1.63)	.07
Rehabilitation facility	2.29 (1.62-3.24)	<.001
Skilled nursing facility	1.43 (1.04-1.96)	.028
Other/against medical advice	0.97 (0.37-2.59)	.96
Hospice	0.60 (0.22-1.68)	.33
Admit service		
Medicine	1 (reference)	
Neurology	0.51 (0.27-0.96)	.037
Surgery	1.22 (0.87-1.71)	.26
Neurosurgery	1.03 (0.54-1.98)	.93
Other	0.32 (0.17-0.60)	<.001
Underwent upper endoscopy		
No	1 (reference)	
Yes	1.70 (1.08-2.66)	.021
No. of discharge medications		
0-7	1 (reference)	
8-10	1.66 (1.29-2.14)	<.001
>10	2.40 (1.88-3.06)	<.001
No. of locations		
1-3	1 (reference)	
4	0.83 (0.64-1.07)	.15
>4	0.70 (0.54-0.91)	.008
Length of stay (d)		
1-7	1 (reference)	
8-15	1.07 (0.82-1.39)	.64
>15	1.56 (1.15-2.12)	.004
Intubated during admission		
No	1 (reference)	
Yes	0.57 (0.44-0.73)	<.001

ICU = intensive care unit; PPI = proton pump inhibitor.

were commonly admitted after cardiac surgery, often still intubated and receiving systemic anticoagulation, and therefore frequently had clear indications for stress ulcer prophylaxis. A total of 98% (1725 of 1765) of CTICU patients were intubated during hospitalization compared with 47% (328 of 693) of cardiac ICU patients, 71%

(320 of 450) of medical ICU patients, and 70% (405 of 582) of surgical ICU patients. Providers may be more likely to discontinue PPI therapy in patients who are started on prophylaxis for an indication with a more defined end point, such as mechanical ventilation, as opposed to coagulopathy or severe sepsis. This is supported by our finding that

a history of mechanical ventilation during admission was a negative risk factor for discharge on inappropriate PPI therapy.

Interestingly, patients inappropriately continued on PPI therapy had a higher mean Charlson Comorbidity Index score on univariable analysis, indicating higher level of illness. However, this association was modest in strength and did not remain significant on multivariable analysis after adjusting for ICU type, length of stay, number of discharge medications, and other significant predictors and was therefore not retained in the final multivariable model. It appears that after adjusting for other variables that also capture the concept of comorbid conditions (eg, length of stay, ICU type, and number of medications), the number of baseline comorbid conditions as measured by the Charlson score may not have a significant impact on whether PPI therapy is inappropriately continued.

Although few outpatient follow-up appointments were available to review, 64% (18/28) of patients discharged on inappropriate PPI therapy were continued on the PPI treatment at follow-up. The ongoing propagation of unnecessary medications may be due to a reluctance by providers to discontinue medications that they did not start. Although PPIs are often considered benign with few side effects, the financial cost of unnecessary PPIs has been well documented.¹⁷⁻²¹ Additionally, although not evaluated in this study, it is also possible that adding an extra unnecessary medication in a medically complex and (likely) overburdened patient can be harmful.^{40,41}

The risk factors for discharge on unnecessary PPI therapy included admission to the surgical ICU compared with the medical ICU, discharge to a rehabilitation or skilled nursing facility, greater number of discharge medications, and greater length of stay. This suggests that provider type and patient medical complexity significantly influence whether unnecessary PPI treatment is continued after an ICU stay. The more floors on which a patient was located during the hospitalization, the less likely they were to

be discharged on PPI therapy. This result may be because a medication reconciliation is required during every patient transfer, and at these times, each medication must be reordered. This provides an additional step (similar to transfer from ICU to floor or floor to discharge) in which providers are prompted to reorder or discontinue medications. Our findings suggest that medication reconciliation, in which providers must review all medications at times of admission, transfer, or discharge, may therefore be a useful tool in eliminating certain unnecessary medications.

We also noted that an upper endoscopy (even in patients without ulcers, *H pylori* infection, esophagitis, Barrett esophagus, or any other clear reasons for acid suppression) is associated with unnecessary PPI use. This may reflect that PPI therapy is often started preemptively in patients with occult GI bleeding or anemia but not stopped after a negative endoscopy result. Gastroenterologists may need to take a more proactive role in recommending the discontinuation of PPI therapy after a negative upper endoscopy result.

The strengths of this study included its large size and the inclusion of multiple ICU types. This study also evaluated risk factors associated with discharge on inappropriate PPI therapy rather than estimating the prevalence of the problem.

A limitation is that it was conducted at a single academic medical center composed of 2 affiliated hospitals. Only a small number of patients had outpatient follow-up records available, so only a subset of charts could be reviewed for ongoing refilling of the PPI after discharge (ie, we did not know how long the PPI treatments were continued in the outpatient setting). It is also important to note that our primary results for predictors of inappropriate PPI therapy continuation were ORs, which can overestimate the risk as the outcome of interest becomes more common. Finally, the classification of PPIs as indicated (or not) relied on the documentation of relevant *International Classification of Diseases* codes.

CONCLUSION

In summary, nearly half the patients who start PPI therapy in the ICU without a long-term indication have the PPI therapy continued on the hospital floor, and more than a quarter are ultimately discharged home on the PPI therapy. Put another way, 16%, or approximately 1 in every 6 patients initiated on PPI therapy in the ICU, are inappropriately continued at hospital discharge. More medically complex patients and those in the surgical ICU were more likely to be discharged on PPI therapy without a documented indication. Encouragingly, some ICU types, for example, cardiac specialty ICUs, started more PPI therapy but were also better at PPI deprescribing. Future quality improvement initiatives can be designed based on these data to reduce the rate of inappropriate PPI prescriptions after ICU stay.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: aOR = adjusted odds ratio; CTICU = cardiothoracic intensive care unit; GI = gastrointestinal; ICU = intensive care unit; OR = odds ratio; PPI = proton pump inhibitor

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