Abstract: Translational Biology Specimen Handling in the ICU: Procedures for a Multicenter Mechanistic Substudy

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Background: Randomized trials suggest that probiotics reduce the incidence of acquired infections in the intensive care unit (ICU), including *Clostridium difficile,* although the mechanisms are not well understood. Our objective was to test the integrity of multi-center multi-specimen procurement, packaging, shipping and analysis in a translational biology study nested within a randomized clinical trial (RCT) in critically ill patients [PROSPECT (Probiotics to prevent Severe Pneumonia and Endotracheal Colonization Trial) NCT00182143].

Methods: From mechanically ventilated patients enrolled in PROSPECT, evaluating *Lactobacillus rhamnosus* GG versus placebo, Hamilton Research Coordinators obtained specimens on the day of enrolment, then each Monday Wednesday and Friday during the patient's ICU stay for the first 30 days, then Tuesday and Thursday thereafter for a maximum of 60 days. Specimens were procured, packaged in biohazard-safe material, then couriered via the inter-hospital within-city specimen transport system (CareCore) to the Surette and Bowdish Laboratories at McMaster University. The following were analyzed: serum endotoxin activity assay and cytokine levels in blood, microorganisms identified by culture-independent techniques in endotracheal aspirates (ETA), bronchial washings (BAL), gastric aspirates (GA) and stool. We estimated on average that each specimen required 5 minutes to procure, package and ship (shipping and processing times were not estimated). Also each day that any specimens were transported, we estimated 5 minutes to communicate with the lab and document specimens on the study log, and 10 minutes to make a return trip with the specimens from the ICU to the transportation office, for every 2 patients with specimens collected on that day.
Results: Overall, 938 samples were procured from 42 patients in 3 ICUs (Table).

SPECIMEN TYPE	# PATIENTS	# SPECIMENS COLLECTED	# SPECIMENS ANALYZED	# SPECIMENS NOT ANALYZED
Endotoxin Assay	41	246	223	23 (Missed 3hr window = 10; No EAA kits = 7; No transport service = 4; No lab staff d/t conference = 2)
Cytokine	42	245	242	3 (No lab staff d/t conference = 2; Missed processing = 1)
ETA	41	225	224	1 (Lost in transit = 1)
BAL	5	8	8	0
GA	37	165	163	2 (Lost in transit = 1; Insufficient quantity = 1)
Stool	21	49	49	0
TOTAL	42	938	909	29

Overall, 909 of 938 (96.9%) of procured specimens were processed. Of the 29 specimens not processed, the reasons were: receipt beyond the 3 hour time frame for valid analyses (10 specimens; no kits available (7); no transportation due to holiday or weather (4) no laboratory staff due to conference (4); lost in transport (2); insufficient quantity (1) and missed (1).
Sending specimens to the central laboratory took ICU Research Coordinators a mean of 58.2 (SD 31.7) minutes (total range 20-180) per specimen collection day per site and mean of 2.9 hours per patient. For 42 patients, 122.2 total hours were spent on specimen procurement, packaging and shipping.

Conclusions: In this 3-center translational study to evaluate the mechanistic impact of probiotics in critically ill patients, excellent organization and communication among research personnel ensured that the analysis yield of nearly 1000 procured specimens was very high. Time-sensitive processing of endotoxin assays was the most common reason for missing data. Evaluating the efforts expended to obtain and process specimens optimally can help to plan sufficient staff and funding to ensure successful collaborative translational biology projects.

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