Use of a sensitive multisugar test for measuring segmental intestinal permeability in critically ill, mechanically ventilated adults : A pilot study

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Abstract

Background: Increased intestinal permeability (IP) is associated with sepsis in the Intensive Care Unit (ICU). This study aimed to pilot a sensitive multi-sugar test to measure IP in critically ill patients in the non-fasted state.

Methods: Critically ill mechanically ventilated adults were recruited from two ICUs in Australia. Measurements were completed within three days of admission using a multi-sugar test measuring gastroduodenal (sucrose recovery), small bowel (lactulose-rhamnose [L-R] and lactulose-mannitol [L-M] ratios) and whole gut permeability (sucralose-erythritol [S-E] ratio) in 24-hour urine samples. Urinary sugar concentrations were compared at baseline and post-sugar ingestion, and IP sugar recoveries and ratios were explored in relation to known confounders including renal function.

Results: Twenty-one critically ill patients (12 males, median 57 years) participated. Group median concentrations of all sugars were higher following sugar administration; however, sucrose and mannitol increases were not statistically significant. Within individual patients, sucrose and mannitol concentrations were higher in baseline than post-sugar ingestion in nine (43%) and four (19%) patients, respectively. Patients with impaired (n=9) versus normal (n=12) renal function had a higher L-R ratio (median 0.130 versus 0.047,p=0.003), a lower rhamnose recovery (median 15 versus 24%,p=0.007) and no difference in lactulose recovery (median 2.5 versus 2.4%,p=0.508).

Conclusion: Small bowel and whole gut permeability measurements are possible to complete in the non-fasted state, while gastroduodenal permeability could not be measured reliably. For small bowel IP measurements, the L-R ratio is preferred over the L-M ratio.

Alterations in renal function may reduce the reliability of the multi-sugar IP test, warranting further exploration.

Clinical Relevancy Statement

Increased intestinal permeability (IP) has been associated with sepsis and multiple organ failure in the Intensive Care Unit (ICU). Limited studies have measured segmental IP in critically ill patients. Early identification of site-specific increases in IP may assist with treatment aimed at reducing mucosal injury and improving outcomes; however, further research is required in this area. Sensitive tests that can be conducted in a non-fasted state are needed, as segmental IP measurements require a longer measurement period compared to traditional small bowel IP tests. This study explores the use of a sensitive multi-sugar test for measuring segmental IP. The findings illustrate that measurements of small bowel and whole gut permeability may be reliable in a non-fasted state. However, our findings support previous concerns that alterations in renal function may confound IP measurements.

Introduction

Critically ill patients frequently experience gastrointestinal dysfunction including increased intestinal permeability (IP), indicative of disrupted intestinal barrier function [1]. Increased IP has been associated with sepsis and multiple organ dysfunction syndrome [2]. The dual sugar absorption test is among the most common non-invasive *in vivo* methods of measuring small bowel IP [3]. This method measures transcellular (using a monosaccharide such as mannitol) and paracellular (using a disaccharide such as lactulose) transport across the intestinal epithelium. Increased IP is reflected by a higher urinary excretion ratio of the disaccharide in relation to the monosaccharide [4-6]. Early identification of increased IP, by comparison to reference ratios from healthy populations, may assist with improving intestinal barrier function and outcomes through potential treatments such as enteral bovine colostrum supplementation [7]; however, further research is needed to inform future management strategies.

Use of the dual sugar absorption test in the Intensive Care Unit (ICU) has been challenged [8,9]. The use of mannitol as a sugar probe has been discouraged due to the presence of this sugar in ICU therapies, for example red blood cell additive solutions [8,9]. Acute kidney injury is a common finding in patients admitted to ICU, and alterations in renal function have been suggested to invalidate the test. The use of lactulose quantities above five grams may decrease intestinal transit times and reduce test sensitivity [8 10]. Lastly, IP measurement is usually preceded by prolonged fasting (≥ five hours), which may interfere with adequate nutrition provision in the ICU.

A sensitive multi-sugar test measuring segmental IP has been validated for use in healthy populations [11, 12]. This test uses smaller quantities of sugars and allows for measurement of gastroduodenal permeability by including sucrose (which is hydrolyzed in the upper part of the small intestine), and whole gut permeability by including erythritol and sucralose (which are resistant to bacterial degradation) [4,11]. Currently there are limited data relating to the application of this method in critically ill patients.

Thus, the aim of this study was to pilot a sensitive multi-sugar test to measure segmental IP in critically ill patients in the non-fasted state. The main objectives were to 1) compare urinary sugar concentrations prior to and following multi-sugar ingestion; and 2) assess measurements in reference to known confounders. We hypothesized that in most patients, there would be sufficient separation in baseline and post-ingestion urinary sugar concentrations to allow assessment of IP in a non-fasted state.

Methods

Patient population

Critically ill mechanically ventilated adults aged 18 years or over and likely to remain in the ICU and on enteral feeding for at least three days were considered for inclusion in the study. A detailed list of eligibility criteria is provided in Supplementary Material (Table S1). Patients were recruited from two hospital tertiary mixed ICUs located in Melbourne, Australia. Patients were recruited over a 24-month period ending in June 2016 at The Alfred Hospital and a 12-month period ending in June 2017 at Footscray Hospital. The study was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12616001101471) and approved by The Alfred Hospital and The Royal Melbourne Hospital Human Research Ethics Committees. Informed consent was obtained from a nominated substitute decision maker.

Measurements of IP were completed in a non-fasted state. All patients were receiving continuous enteral nutrition using polymeric formulas prescribed by the unit dietitian and medical team. Nutrition adequacy, expressed as a percentage of the amount of delivered energy and protein in comparison with prescribed values, was recorded at the time of the IP measurement. Delivered nutrition was calculated by considering all provided enteral nutrition formula minus any discarded gastric residual volumes or vomit within each 24-hour period. The prescription of non-nutritional sources of energy (e.g. propofol administration) was considered in order to accurately calculate energy adequacy.

Intestinal permeability measurement

A multi-sugar test based on the method detailed by van Wijck et al was used to measure segmental IP within the first three days of ICU admission [11]. The sugars consisted of 1 g sucrose, 0.5 g L-rhamnose, 1 g lactulose, 1 g erythritol, and 1 g sucralose. Additionally, 1 g of mannitol was added to allow for comparison of the lactulose-rhamnose (L-R) and lactulose-mannitol (L-M) ratios as measures of small bowel IP. Figure 1 depicts the sugars used for the measurement of segmental IP.

Prior to commencing the IP test, baseline concentrations of the test sugars were analyzed in 50 mL urine samples. Test sugars dissolved in 50 mL of potable water were then administered via a nasogastric tube in place for enteral feeding. Urine was collected for the subsequent 24-hour period, referred to as the 'post-sugar ingestion' collection. Gas chromatography-mass spectrometry was used to analyze sugar concentrations in urinary baseline and test samples. Analyses were conducted by Metabolomics Australia at The University of Melbourne, a National Collaborative Research Infrastructure Strategy (NCRIS) initiative under Bioplatforms Australia Pty Ltd according to a previously published method [13].

The 24-hour urinary excretion and percentage recovery of each sugar was calculated using the following formulae:

(1) Urinary excretion of sugar (μmol) = concentration of sugar in urine (μmol/L) x total 24-hour volume of urine (L).

(2) Percentage urinary recovery of sugar = (urinary excretion of sugar [μmol]/ quantity of sugar ingested [μmol]) x 100.

Comparison of baseline and post-ingestion urinary sugar concentrations

Baseline and post-ingestion urinary sugar concentrations (μmol/L) were compared and considered to be reliable to interpret if 1) the group median increased following sugar administration and 2) there was no overlap between baseline and post-ingestion urinary concentrations of sugars within individual patients.

Intestinal permeability measurement and confounders

Possible confounders of IP measurements were additionally measured during the 24-hour urine collection, including total urinary volume, hypotension (lowest mean arterial pressure), hypoxemia (lowest partial pressure of oxygen in arterial blood [PaO_2]), acidosis (lowest pH), hemoglobin concentration (lowest hematocrit) and renal function (impaired renal function defined as a glomerular filtration rate [GFR] below 90 mL/min/1.73m^2). Blood cell transfusions within 24 hours of commencing or during the IP test were also recorded [8,9].

Sample size

As no previous study has used a comparable multi-sugar IP test in critically ill patients, there were no data available to complete a sample size calculation. A convenience sample of 20-30 patients was targeted as the number of patients feasible to recruit during the study timeframe. This number was also considered to provide adequate pilot data to explore whether the multi-sugar test could be used reliably in a non-fasted state.

Statistical analyses

All statistical analyses were conducted using IBM® SPSS® Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp). Normality tests were performed using the Shapiro-Wilk test, with means ± standard deviation (SD) or medians and [interquartile range] (IQR) used to describe data according to distribution. When comparing related variables, a Paired Samples *t* test or Wilcoxon Signed-Rank test was used. When comparing two independent variables, the Independent-Samples *t* Test or Mann-Whitney U test was used. Correlation analyses were used to explore associations between IP measurements (percentage recovery of sugars and IP ratios) and potential test confounders, with the Pearson correlation coefficient or Spearman Rho Test used. A two-tailed *p*-value less than 0.05 was considered statistically significant.

Results

During the recruitment period, 22 critically ill patients were consented, with 21 included in analysis (Figure 2). Patients were predominantly male (57%) with a median age of 57 [37-63] years, mean APACHE II score of 19 ± 5 and admitted for management of trauma-related injuries (38%). Further patient demographics are displayed in Table 1. At the time of the IP measurement, the mean daily delivered energy was 1329 ± 477 kcal (1428 ± 482 kcal including propofol) and 61 ± 22 g of protein. This corresponded to 69 ± 23% (76 ± 23% including propofol) and 65 ± 23% of prescribed energy and protein daily targets, respectively.

Intestinal permeability measurements

Segmental IP measurements were completed on ICU admission day 2.5 ± 0.7. Two measurements were completed outside of the intended first three days but within four days of ICU admission. The percentage recovery of mono- and disaccharides were higher for sugars reflective of whole gut permeability (erythritol and sucralose) in comparison to sugars reflective of gastroduodenal and small bowel IP (sucrose, rhamnose, mannitol and lactulose) (Table 2). The L-R and L-M ratios, both measures of small bowel IP, differed significantly (median 0.055 [0.032-0.108] versus 0.025 [0.016- 0.045], respectively, p <0.001).

Comparison of baseline and post-ingestion urinary sugar concentrations

Monosaccharides mannitol and erythritol were detected in all (100%) baseline urine samples, while rhamnose was detected in nine (43%) samples. Disaccharides sucrose,

lactulose and sucralose were detected in 19 (90%), six (29%) and one (5%) baseline urine sample, respectively.

Group median concentrations of all sugars were higher following test sugar administration; the increases in sucrose and mannitol did not reach statistical significance (Figure 3) (Table S2). Within individual patients, no overlap between baseline and post-sugar ingestion concentrations were noted for rhamnose, erythritol and sucralose. Conversely, concentrations of sucrose, mannitol and lactulose in baseline samples were higher than post-sugar ingestion in nine (43%), four (19%) and one (5%) patient, respectively.

Intestinal permeability measurement and confounders

No significant associations between IP measurements and urinary volume, PaO_2, mean arterial pressure, hematocrit and pH were noted (Table S3). Seven patients (33%) received red blood cell transfusions. The percentage recovery of mannitol and L-M ratio did not differ in patients who received versus those who did not receive transfusions (data not shown). Nine patients were recorded as having impaired renal function. Patients with impaired versus normal renal function were found to have significantly higher L-R (median 0.130 versus 0.047, respectively, p=0.003) and L-M ratios (median 0.046 versus 0.020, respectively, p=0.012), with no differences found for the S-E ratio (median 0.032 versus 0.022, respectively, p=0.169). When explored further, the percentage recovery of monosaccharides rhamnose and erythritol was lower in patients with impaired versus normal renal function; rhamnose (mean 14.5% versus 23.9%, respectively, p=0.007) and erythritol (mean 59.8% versus 96.6%, respectively, p=0.005). No differences were observed for the percentage recovery of mannitol (median 46.8% versus 55.3%, respectively, p=0.169), or disaccharides

lactulose (median 2.5 versus 2.4%, respectively, *p*=0.508) and sucralose (mean 6.0 versus 7.5%, respectively, *p*=0.155).

Discussion

Key Findings

In this two-center pilot study of mechanically ventilated critically ill adult patients, we found that measurements of small bowel IP and whole gut permeability were possible using a sensitive, multi-sugar test in a non-fasted state. Baseline urinary concentrations of sugars from enteral and/or endogenous sources were frequently detected prior to the completion of IP measurements. However, median concentrations were higher following sugar solution administration for all sugars; but increases in sucrose and mannitol were not statistically significant. The measurement of gastroduodenal permeability using sucrose was not considered reliable in a non-fasted state. The results of the L-R and L-M ratios, both commonly used as measures of small bowel IP, varied substantially. Impaired renal function was associated with a decreased recovery of rhamnose and erythritol and an increased L-R and L-M ratio, raising concerns regarding the reliability of IP measurements in this subgroup.

Comparison of baseline and post-ingestion urinary sugar concentrations

Baseline urinary sugar concentrations prior to IP measurement are rarely reported, with the assumption made that concentrations are undetectable following a protocolized fasting period. In our study, baseline urinary concentrations of sugars were frequently detected. This is consistent with findings by van Wijck et al where segmental IP was measured in ten healthy participants fasted from food and drinks for ten hours overnight on four separate test days. Interestingly, baseline urinary sugar concentrations reported were comparable

(mannitol was the only sugar not analyzed in this study) and in some instances higher than our findings, despite being measured in a fasted state [11]. This supports the notion that sugars may be present in small quantities in medications and/or may be produced endogenously. For this reason, baseline sugar concentrations should be analyzed when measuring IP using the sugar-absorption test to assist with the interpretation of measurements.

Despite frequent detection, baseline concentrations of sugars were overall low and increased significantly following administration of the sugar solution for all sugars excluding mannitol and sucrose. Despite not being listed as an ingredient, the manufacturer of the enteral nutrition formulae confirmed that products contained 0.05 g of sucrose per 100 mL (personal communication), which although small, likely interfered with the measurement of gastroduodenal permeability in our study. Sucrose should not be used as a sugar probe for the measurement of gastroduodenal permeability in future unless patients are fasted prior to IP testing, in cases where the administered enteral nutrition formula does not contain sucrose and if baseline urinary sugar analysis confirms that background concentrations are low and not comparable with post-sugar ingestion concentrations. In our study, mannitol was detected in all baseline urine samples, independently of red blood cell transfusions. This suggests that mannitol may be present in small amounts in medications, enteral nutrition formula and/or may be produced endogenously [5,10]. Baseline concentrations of mannitol also displayed greater variability when compared to rhamnose, both used as markers of transcellular small bowel IP. The results of this study together with those from previous ICU studies [8,9] support the use of rhamnose as a marker of transcellular small bowel IP, in preference to mannitol. Further, our results highlight that the L-R and L-M, despite both

providing an indication of small bowel IP are likely to vary. This should be considered when interpreting findings of previous studies.

Intestinal permeability measurement and confounders

In our study, impaired renal function was associated with decreased recoveries of rhamnose and erythritol and subsequently higher L-R and L-M ratios. This supports findings of Oudemans-van Straaten et al, who measured gastroduodenal and small bowel IP in 64 mechanically ventilated patients with multiple organ dysfunction syndrome within 24 hours of admission [8]. The authors found that recoveries of disaccharides sucrose and cellobiose were positively related to creatinine clearance, whereas no relationship between the recovery of the monosaccharide mannitol and creatinine clearance was apparent. The authors concluded that post-mucosal factors, such as renal function, may affect the recovery of mono- versus disaccharides differently, challenging the underlying assumptions of the sugar absorption test [8]. This raises concerns regarding the reliability of IP measurements in patients with impaired renal function. However, findings need to be explored and confirmed in larger populations.

Strengths and limitations

The strengths of this study include the measurement of segmental IP using a sensitive multi-sugar test. The low sugar dose used (5.5 g in total) is likely to have minimized the effects of the sugar solution on intestinal transit [14]. The collection and analysis of baseline urinary concentrations of sugars assists the interpretation of IP analysis. This data is often not collected or reported in IP studies, making it difficult to accurately interpret IP measurements in previous studies. In the ICU, all urine produced during the 24-hour measurement period

was collected and confounders were explored, which is rare among those few papers exploring IP in critically ill populations. The limitations of this study include the assumption that 50 ml baseline spot urine samples are reflective of concentrations in 24-hour baseline collections, which needs to be first established. In this study, renal function was measured using routinely available laboratory markers and age-associated loss of kidney function was not considered. Although patient characteristics in this study are comparable with Australian and New Zealand ICU populations [15], findings should be interpreted with caution due to the small sample size, particularly when exploring the segmental IP test in relation to test confounders.

Future directions

As renal impairment affects a significant proportion of critically ill patients, the reliability of IP measurements using the dual or multi-sugar method needs to be confirmed in this subpopulation [16]. To enhance interpretation, intestinal barrier function could be further explored by use of the sugar-absorption IP test in combination with measures reflective of overall gastrointestinal barrier function that do not require urinary volume collections; such as markers of intestinal epithelial tight junction integrity (e.g. urinary concentration of Claudin proteins [i.e. Claudin-3]), indicators of functional enterocyte mass (e.g. plasma citrulline) and enterocyte cell damage (e.g. intestinal fatty acid binding proteins [I-FABPs]) [17-19].

Conclusion

Small and whole gut permeability measurements can be completed in a non-fasted state in mechanically ventilated critically ill patients using a sensitive multi-sugar test. Gastroduodenal permeability could not be measured accurately in the present study, owing to the presence of sucrose in enteral nutrition formula, which interfered with measurements. The L-R ratio was considered to provide a more reliable measure of small bowel IP in comparison to the L-M ratio. Alterations in renal function may affect the sugar recovery of mono- versus disaccharides differently, reducing the reliability of the multi-sugar IP test in this subpopulation, warranting further exploration.

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Supplementary Material: Please access supplementary material online.

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Figure 1. Measurement of segmental intestinal permeability†

IP, intestinal permeability; L-M, lactulose-mannitol; L-R, lactulose-rhamnose; S-E, sucralose-erythritol.

†Creative commons licence (https://pixabay.com/en/offal-marking-medical-intestine-1463369/): Free for commercial use. No attribution required. Figure adapted.

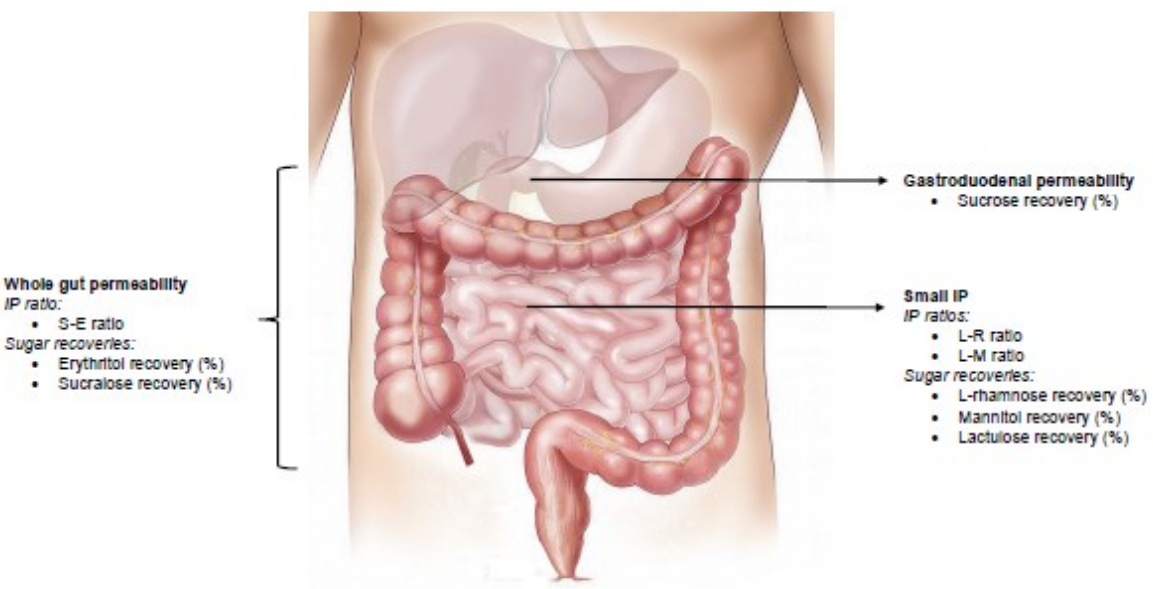


Figure 2. Study flow diagram

IP, intestinal permeability

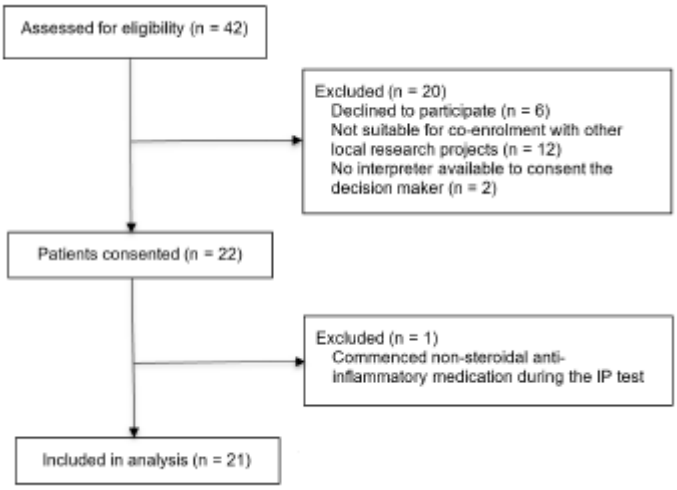
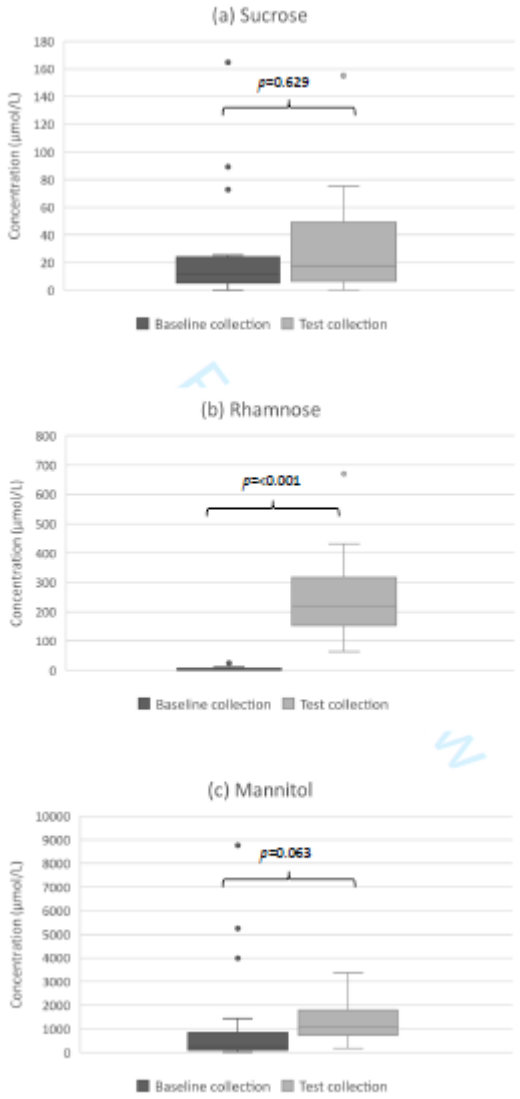
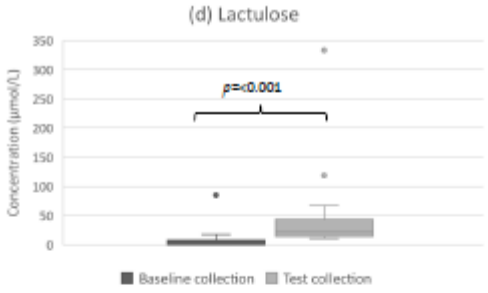
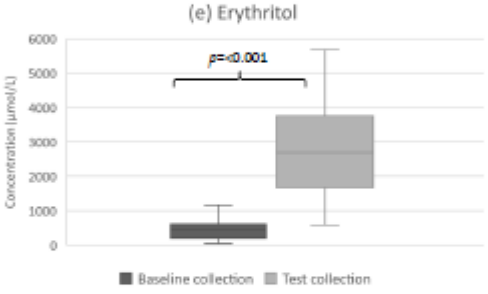


Figure 3. Box plots depicting the variation in sugar concentrations between baseline (50 mL samples) and test (post-sugar ingestion 24-hour collections) urine samples in critically ill patients. Urinary concentration (µmol/L) for (a) sucrose, (b) rhamnose, (c) mannitol, (d) lactulose, (e) erythritol, (f) sucralose

° Indicates outliers







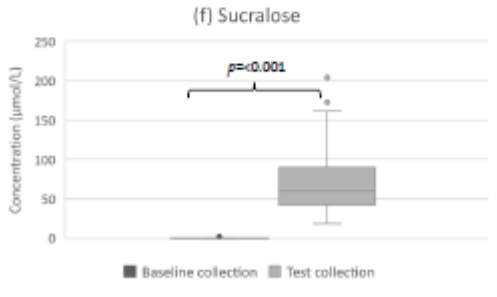


Table 1. Characteristics of critically ill patients

Variable	Critically ill patients (n=21)
Sex, male/female, n	12/9
Age, years, median [IQR]	57.0 [37.0-62.5]*
Weight, kg, median [IQR]	85.0 [71.5-100.0]*
Height, m, mean ± SD	1.71 ± 0.10
BMI, kg/m^2, median [IQR]	27.2 [23.9-34.9]*
Diagnoses, n (%)	
Cardiac	4 (19.0)
Neurological	4 (19.0)
Respiratory	3 (14.3)
Sepsis	2 (9.5)
Trauma	8 (38.1)
APACHE II, mean ± SD	19.1 ± 5.4

* Non-parametric variables

APACHE, Acute physiology and chronic health evaluation; BMI, body mass index.

Table 2. Intestinal permeability ratios and urinary sugar recoveries

Variable	IP test, n= 21
Urinary volume, L, median [IQR]	2.6 [1.5-4.6]*
L-R ratio, median [IQR]	0.055 [0.032-0.108]*
L-M ratio, median [IQR]	0.025 [0.016- 0.045]*
S-E ratio, median [IQR]	0.027 [0.018- 0.035]*
Sucrose recovery, %, median [IQR]	1.6 [0.6-2.3]*
Rhamnose recovery, %, mean ± SD	17.5 ± 11.5
Mannitol recovery, %, median [IQR]	53.9 [38.9- 64.7]*
Lactulose recovery, %, median [IQR]	2.5 [1.5-2.9]*
Erythritol recovery, %, mean ± SD	80.8 ± 28.4
Sucralose recovery, %, mean ± SD	6.9 ± 2.4

* Non-parametric variables

IQR, interquartile range; L-M, lactulose-mannitol; L-R, lactulose-rhamnose; S/E, sucralose-erythritol; SD, standard deviation.