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The measurement of intestinal permeability in critically ill patients

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Background

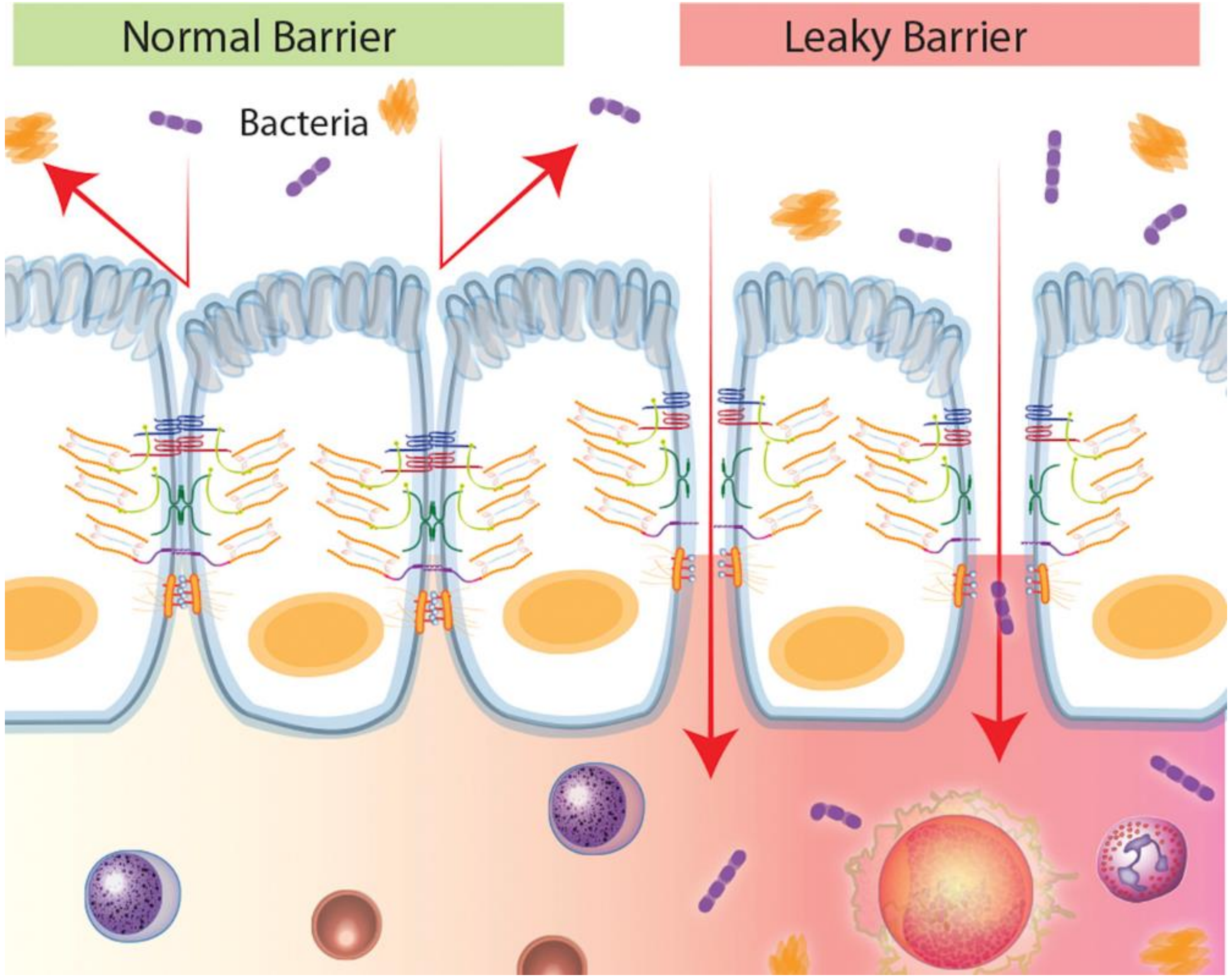
Intestinal permeability

- The GI tract is important to protect the body from the entry of harmful substances (e.g. bacteria, toxins)
- This is known as the intestinal barrier function
- Intestinal permeability (IP) provides a measure of the intestinal barrier function

Bischoff SC, Barbara G, Buurman W, Ockhuizen T, Schulzke JD, Serino M, et al. Intestinal permeability--a new target for disease prevention and therapy. BMC gastroenterology. 2014;14:189.

Measurement of intestinal permeability

- The current non-invasive *in vivo* gold standard method of measuring IP is the dual sugar test
- The test assesses the ability of inert sugars to cross the mucosal (epithelial) lining of the GI tract via:
  - Transcellular route (assessed using monosaccharides)
  - Paracellular route (assessed using disaccharides)
  - Increased IP is reflected by an increase in paracellular compared to transcellular permeability
- Based on the assumption that pre- (e.g. gastric emptying) and post- (e.g. renal function) mucosal factors equally affect the urinary excretion of mono- and disaccharides.



- Bjarnason I, Macpherson A, Hollander D. Intestinal permeability: An overview. Gastroenterology. 1995;108(5):1566-81.
- Stewart AS, Pratt-Phillips S, Gonzalez LM. Alterations in Intestinal Permeability: The Role of the “Leaky Gut” in Health and Disease. Journal of Equine Veterinary Science. 2017;52:10-22.

Intestinal permeability in the ICU

- In the 1990s, studies in the ICU suggested that small IP is increased in critical illness and linked with complications including sepsis
- However, concerns re: the use of the dual sugar IP test in the ICU were raised due to:
  - Alterations in renal function were found to affect the excretion of mono- and disaccharides differently
  - Mannitol was used in red blood cell additive solutions
- No further studies have measured IP in relation to possible test confounders or evaluated newer sensitive multi-sugar IP tests in the ICU setting.

- Oudemans-van Straaten HM, et al. Pitfalls in gastrointestinal permeability measurement in ICU patients with multiple organ failure using differential sugar absorption. Intensive care medicine. 2002;28(2):130-8.
- De-Souza, et al. Intestinal permeability and systemic infections in critically ill patients: effect of glutamine. Crit Care Med. 2005;33(5):1125-35.

Aim

To investigate the relationship between segmental IP measured using a sensitive multi-sugar test, renal function and potential test confounders in critically ill mechanically ventilated patients

Method

Method

- Critically ill adult patients were recruited from The Alfred (Alfred Health) and Sunshine (Western Health) ICUs in Melbourne, Australia
- The IP measurement was completed within 72 hours of ICU admission
- Aim was to recruit 20-30 patients

Inclusion criteria	Exclusion criteria
• Adult patients (≥18 years of age) • Receiving or suitable for enteral nutrition • Likely to require MV for >24 hours • Receiving inotropic or vasopressor support at time of enrolment	• History of GI conditions • Admitted with abdominal trauma • Receiving CRRT • Treatment with NSAIDs or any of the test sugars administered as part of the IP measurement

- Ethics approval was granted from Alfred Hospital Ethics Committee and Melbourne Health Human Research Ethics Committee

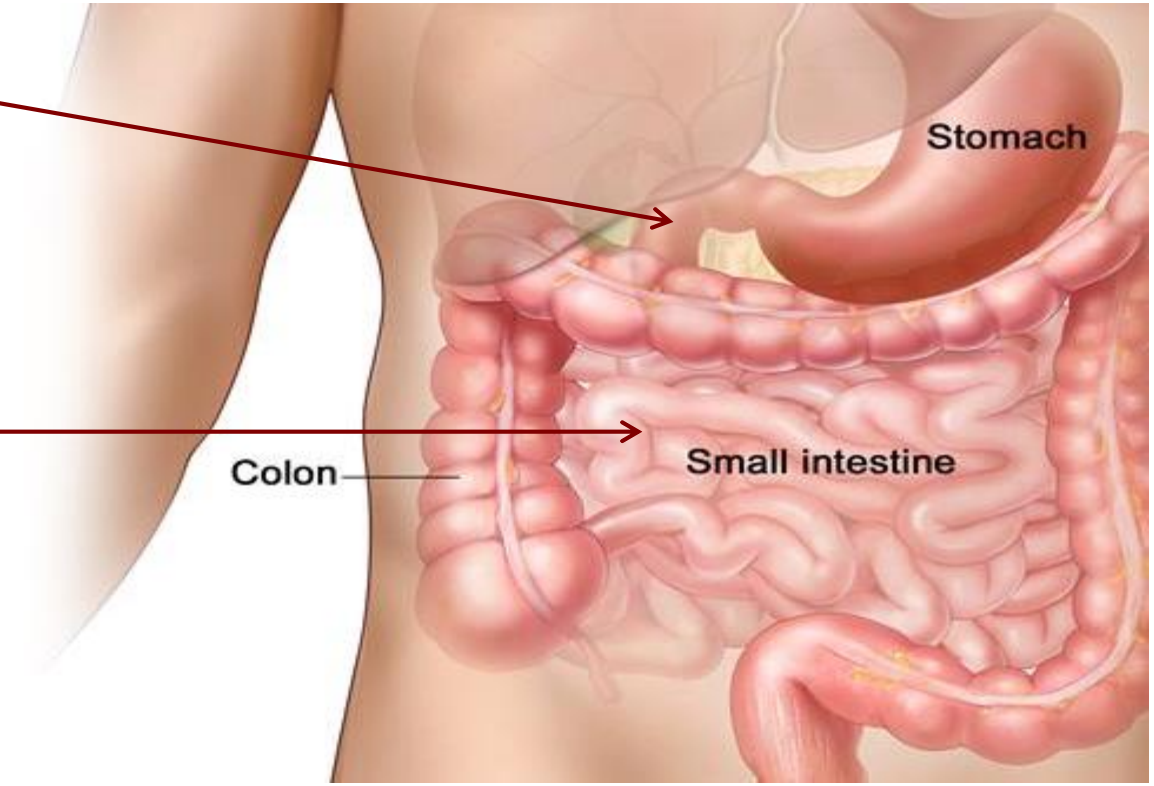
Measurement of IP

- 1 g sucrose, 0.5 g L-rhamnose, 1 g lactulose, 1 g erythritol and 1 g sucralose were dissolved in 50 ml of water and administered as a flush via the NG tube
- Gas chromatography-mass spectrometry was used to analyse sugar concentrations in 0-24 hour urine samples

Gastroduodenal IP:
- % recovery of sucrose
- Short-lived in the upper part of the duodenum

Small IP:
- Lactulose/rhamnose ratio (L-R ratio)
- % recovery of rhamnose (transcellular transport)
- % recovery of lactulose (paracellular transport)
- The above sugars are fermented when reaching the colon

Whole gut permeability:
- Sucralose/erythritol ratio (S-E ratio)
- % recovery of erythritol (transcellular transport)
- % recovery of sucralose (paracellular transport)
- Not metabolised by gut bacteria in the GI tract



- Arrieta MC, et al. Alterations in intestinal permeability. Gut. 2006;55(10):1512-20.
- van Wijck K, et al. Novel analytical approach to a multi-sugar whole gut permeability assay. Journal of Chromatography B. 2011;879(26):2794-801.

During the 24-hour urine collection, the following variables were collected to determine if there was an association between IP measurements and:

Renal function

- Lowest glomerular filtration rate (eGFR)
- Highest creatinine
- Total urinary volume

Potential confounding variables

- Hypotension (lowest mean arterial pressure [MAP])
- Hypoxaemia (lowest partial pressure of oxygen in arterial blood [PaO_2])
- Acidosis (lowest pH)

Oudemans-van Straaten HM, et al. Pitfalls in gastrointestinal permeability measurement in ICU patients with multiple organ failure using differential sugar absorption. Intensive care medicine. 2002;28(2):130-8.

Results

Patient characteristics

Variable	Critically ill patients (n = 21)
Sex, male/female	12/9
Age, years, median (IQR)	57.0 (26.0)
BMI, kg/m^2, median (IQR)	27.2 (11.1)*
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
APACHE III, mean ± SD	61.8 ± 25.1
SOFA score $_{0-24}$, median (IQR)*	10.0 (2.0)*

* Non-parametric variables

No significant associations were observed between the % recovery of mono- and disaccharides and small and whole gut IP ratios and:

- Urinary volume
- Lowest MAP
- Lowest PaO_2
- Lowest pH

All *p*-values > 0.05

Renal function

Glomerular filtration rate

- Impaired GFR = <90 mL/min/1.73m^2
- Normal GFR = ≥90 mL/min/1.73m^2

	Normal renal function n = 12	**Impaired renal function n = 9**	***p*-value**
% recovery of L-rhamnose, mean (SD)	24 ± 15	15 ± 7	**0.007**
% recovery of lactulose, mean (SD)	2 (1)	3 (4)	0.508
% recovery of erythritol, mean (SD)	97 ± 15	60 ± 29	**0.005**
% recovery of sucralose, mean (SD)	8 ± 2	6 ± 3	0.155
L-R ratio, median (IQR)	0.047 (0.025)	0.130 (0.126)	**0.003**
S-E ratio, median (IQR)	0.022 (0.016)	0.032 (0.023)	0.169

Discussion

- In this study, no associations were found between IP measurements and urinary volume, PaO_2, MAP and pH.
- However, patients with impaired renal function had decreased recoveries of mono- versus disaccharides.
- These findings support previous results that renal impairment affects the recovery of mono- and disaccharides differently in the ICU.
- This violates one of the central underlying assumptions of the IP sugar test.
- As impaired renal function is common in ICU patients, more reliable measurement tools are needed to measure IP in patient group.
- Findings from previous ICU studies measuring IP using the dual or multi sugar test should be interpreted with caution.

Oudemans-van Straaten HM, et al. Pitfalls in gastrointestinal permeability measurement in ICU patients with multiple organ failure using differential sugar absorption. Intensive care medicine. 2002;28(2):130-8.

Conclusion

- Alterations in renal function affects the recovery of transcellular versus paracellular permeability sugar probes differently in ICU patients.
- More simplistic and reliable tools that are not dependent on urine collections are needed to measure IP in the ICU setting.

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Thank you

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Renal function

Creatinine

- **A significant negative association** was observed between the highest creatinine concentration and:
  - % recovery of L-rhamnose (small intestine transcellular transport) *r* -0.618, *p* 0.003
  - % recovery of erythritol (whole gut transcellular transport) *r* -0.489, *p* 0.025
  - The L-R ratio (marker of small IP) *r* 0.481, *p* 0.027
- **No significant associations were observed** between markers of paracellular transport (% recovery of lactulose and sucralose) and whole gut permeability (S-E ratio)

  (*p* values> 0.05)

IP measurements

Variable	IP test, n= 21
Urinary volume, L, median (IQR)	3 (3)*
L-R ratio, median (IQR)	0.055 (0.076)*
S-E ratio, median (IQR)	0.027 (0.017)*
Sucrose recov[illegible]%, median (IQR)	2 (2)*
L-rhamnose recovery, %, mean ± SD	18 ± 12
Erythritol recovery, %, mean ± SD	81 ± 28
Lactulose recovery, %, median (IQR)	3 (1)*
Sucralose recovery, %, mean ± SD	7 ± 2

* Non-parametric variables