KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Intestinal Permeability Assessment Interpretation Guide

There are two primary methods used clinically to assess leaky gut: the lactulose/mannitol permeability assay (through Genova, covered here), and the antigenic permeability screen (Cyrex Array 2, covered in another handout).

The lactulose/mannitol test measures levels of both sugars in a patient's urine after oral ingestion. Lactulose and mannitol are both oligosaccharides. Their differing molecular weights help determine if permeability is transcellular or paracellular.

- Mannitol
    - Small enough to pass through the cell (transcellular).
    - Weighs 182 daltons with a molecular radius up to 0.4 nanomicrons.
- Lactulose
    - Larger size means it passes between cells (paracellular).
    - Weighs 342 daltons with a molecular radius of 0.42 nanomicrons.

In a healthy person, mannitol is expected to be measured in larger amounts, due to its small size, normally from 10 to 30 percent of the orally ingested dose. Lactulose would be expected to be recovered at only about 1 percent of the oral dose due to its larger size.

Gut barrier integrity depends on the proper functioning of the intercellular tight junctions and should therefore limit transit via the paracellular route. A higher lactulose-to-mannitol ratio is indicative of intestinal permeability. The changed ratio can have several causes:

- Increased lactulose absorption via the paracellular route. This may be due to decreased villous height or impaired function of tight junctions.
- Decreased mannitol absorption due to decreased surface areas of gut villi.

Causes of Intestinal Permeability

- Gut pathology
- Metabolic dysfunction
    - Obesity
    - Higher insulin levels

A major critique of this test is that transport of these molecules through the barrier is not necessarily an indicator for tight junction malfunction. There are many other factors that influence uptake, such as GI motility, smoking, medications, etc. Additionally, only molecules over 5,000 daltons can change intestinal permeability and result in T-cell response. Since these molecules are much smaller, they may not be appropriate challenge molecules.

LACTULOSE/MANNITOL TEST INTERPRETATION MATRIX

Analyte	Result	Analyte	Result	Analyte	Result	Indication
Lactulose	High	**Mannitol**	Normal	**L/M Ratio**	High	**Increased IP**
Lactulose	High	**Mannitol**	Low	**L/M Ratio**	High	**Increased IP + malabsorption**
Lactulose	High	**Mannitol**	High	**L/M Ratio**	Normal	**Increased IP d/t insulin resistance**
Lactulose	Normal	**Mannitol**	Normal	**L/M Ratio**	Normal	**Normal IP**
Lactulose	Normal	**Mannitol**	Low	**L/M Ratio**	High	**Malabsorption**
Lactulose	Normal	**Mannitol**	High	**L/M Ratio**	Low	**↑ transcellular permeability**
Lactulose	Low	**Mannitol**	High	**L/M Ratio**	Low	**↑ trans ↓ para permeability**
Lactulose	Low	**Mannitol**	Normal	**L/M Ratio**	Low	**↓ paracellular permeability**
Lactulose	Low	**Mannitol**	Low	**L/M Ratio**	Normal	**Malabsorption?**