Raw Milk, Two E. coli O157:H7 Outbreaks, and hemolytic uremic syndrome (HUS): what are the real acute and long-term consequences? - Part 1

Posted by Bill Marler on April 23, 2012

With E. coli O157:H7 outbreaks in Missouri and Oregon linked to raw milk consumption, and perhaps as many as five children struggling for life – and hopefully surviving the acute phase of their illnesses – the long-term risk of kidney complications for these kids is a real concern. Here is an overview of hemolytic uremic syndrome (HUS) induced renal injury. A more complete picture can be seen at www.about-hus.com.

Part 1 – Acute hemolytic uremic syndrome (HUS)

Post-diarrheal hemolytic uremic syndrome (D+HUS) is a severe, life-threatening complication that occurs in about 10 percent of those infected with E. coli O157:H7 or other Shiga toxin- (Stx-) producing E. coli.

The chain of events leading to HUS begins with ingestion of Stx-producing E. coli (e.g., E. coli O157: H7) in contaminated food, beverages, animal to person, or person-to-person transmission.

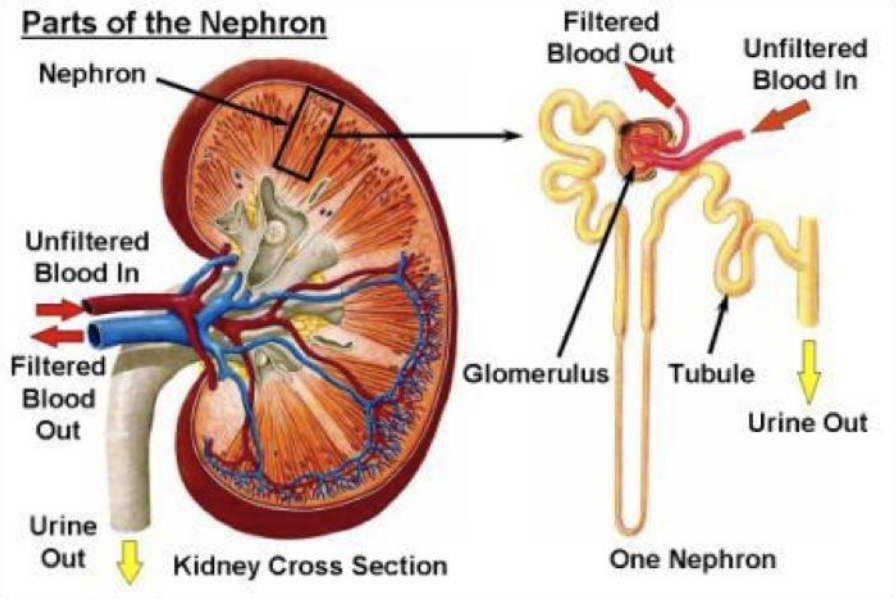
These E. coli rapidly multiply in the intestine causing colitis (diarrhea), and tightly bind to cells that line the large intestine. This snug attachment facilitates absorption of the toxin into the intestinal capillaries and into the systemic circulation where it becomes attached to weak receptors on white blood cells (WBC) thus allowing the toxin to "ride piggyback" to the kidneys where it is transferred to numerous avid (strong) Gb3 receptors that grasp and hold on to the toxin.

Organ injury is primarily a function of Gb3 receptor location and density. Receptors are probably heterogeneously distributed in the major body organs, and this may explain why some patients develop injury in other organs (e.g., brain, pancreas).

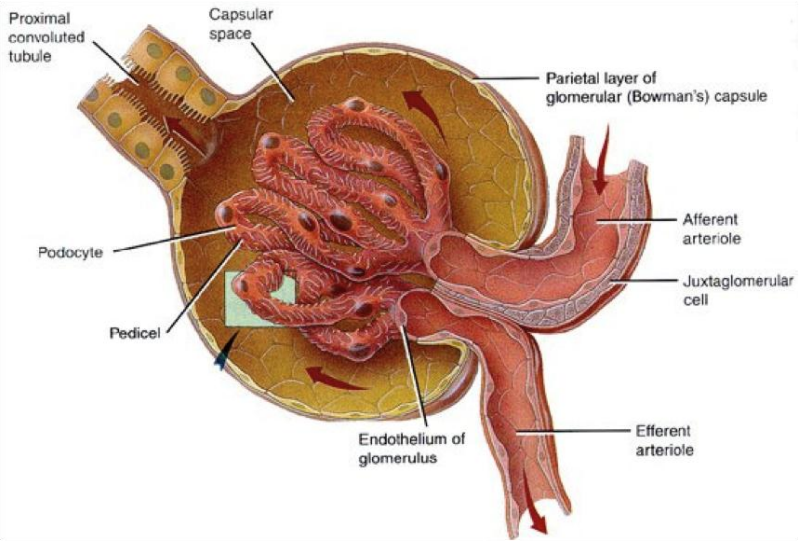
Once Stx attaches to receptors, it moves into the cell's cytoplasm where it shuts down the cells' protein machinery resulting in cellular injury and/or death. This cellular injury activates blood platelets and the coagulation cascade, which results in the formation of clots in the very small vessels of the kidney, resulting in acute kidney injury and failure.

The red blood cells undergo hemolytic destruction by Stx and/or damage as they attempt to pass through partially obstructed microvessels. Blood platelets (required for normal blood clotting), are trapped in the tiny blood clots or are damaged and destroyed by the spleen.

Each kidney has between 700,000 and 1,000,000 filtering units, called “nephrons.” The heart of each filter is a microscopic bundle of blood vessels called glomeruli. Blood goes into each glomerulus and waste products pass through a membrane into tubules, which connect together and ultimately collect the urine and pass it out of the kidney. Here is a normal kidney:

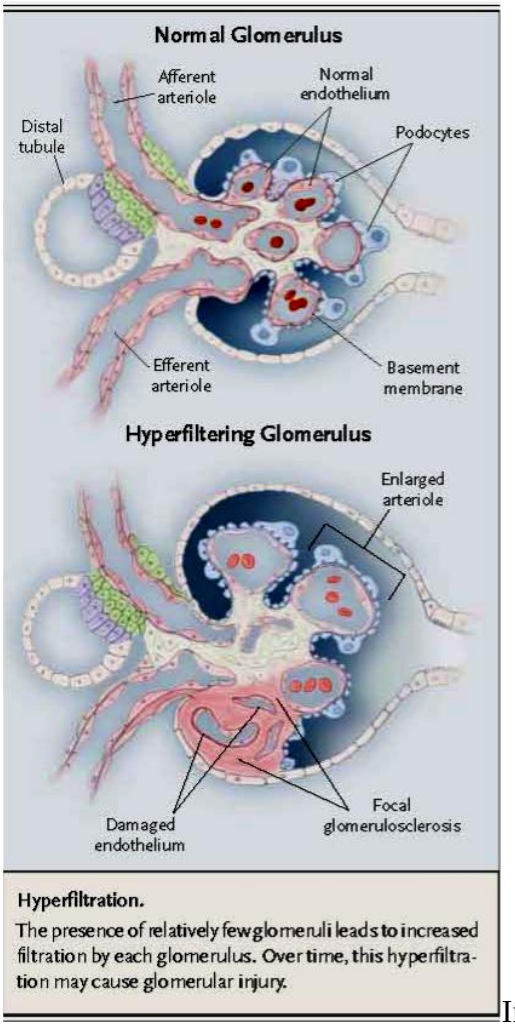


If we zoom in on the microscopic glomerulus:



The glomerulus is the main filter of the nephron and is located within the Bowman's capsule. The glomerulus resembles a twisted mass of tiny tubes through which the blood passes. The glomerulus is semipermeable, allowing water and soluble wastes to pass through and be excreted out of the Bowman's capsule as urine. The filtered blood passes out of the glomerulus into the efferent arteriole to be returned through the medullary plexus to the intralobular vein.

Meanwhile, the filtered water and aqueous wastes are passed out of the Bowman's capsule into the proximal convoluted tubule.



Hyperfiltration.
The presence of relatively few glomeruli leads to increased filtration by each glomerulus. Over time, this hyperfiltration may cause glomerular injury.

In HUS, a certain number of glomeruli are permanently damaged due to loss of blood flow as tiny thrombi occlude those blood vessels. The toxins from E. coli O157:H7 also have a direct effect on the cells lining the blood vessels and tubules and can cause cell death. Once a filter is gone, it is gone forever. When a lot of filters are gone, the remaining ones work harder because there are fewer of them. If enough filters are lost, the remaining filters experience “hyperfiltration,” which leads to enlargement, and over time, scarring, which in turn leads to the loss of more filters.

Serious kidney injury usually manifests through reduced filter function, hypertension, and/or proteinuria. It is easy to get a rough estimate of kidney filter function by looking at the level of waste products, especially creatinine in the blood over time. There are also formulas to estimate filter function once you have a creatinine value. The key is whether filter function changes over time. Since the kidneys primarily regulate blood pressure, the development of hypertension after HUS also signals serious kidney injury and is considered a bad prognostic sign. So too is proteinuria—the passage of protein molecules in the urine—which is a sign that the glomeruli

have been damaged, and the remaining filters are hyperfiltrating—i.e. they are being overworked due to the loss of filtering capacity of other dead or damaged filters.

If enough filters are lost either due to injuries suffered during the acute HUS illness, or later in life due to the process of hyperfiltration, a patient will reach end stage renal disease ("ESRD"). ESRD, truly a worst-case scenario for someone who has survived the acute HUS illness, is a very painful process that can take decades to play out. The demands on the kidneys increase through puberty and, for women, especially during pregnancy, adding another variable to issues of future renal health for girls who have suffered severe HUS.

Tomorrow **Part 2 – Long-term consequences of hemolytic uremic syndrome (HUS)**