Shiga Toxin Producers

Shiga toxin-producing *Escherichia coli* (STEC) derive their name from the ability to produce toxins (Stx1 & Stx2) similar in structure and function to Shiga toxin produced by *Shigella dysenteriae.* STEC infections are associated with gastrointestinal diseases and have been linked to hemorrhagic colitis and hemolytic uremic syndrome (HUS). Transmission of STEC primarily occur through the consumption of contaminated foods and causes approximately 100,000 illnesses, 3,000 hospitalizations, and 90 deaths annually in the United States, according to a 1999 estimate (1). According to the CDC and a study conducted by the Michigan Department of Community Health, most STEC isolates are recovered between the months of June and October although the transmission of STEC can happen at any time of year (2). Young children and elderly persons are at the greatest risk of a STEC infection, although healthy adults may be asymptomatic carriers.

The key virulence factors of STEC are the Shiga toxins. Shiga toxin 1 (Stx1) is very similar in amino acid sequence to the Shiga toxin produced by *Shigella dysenteriae*, and is neutralized by antibodies against the *S. dysenteriae* toxin. Stx1 is approximately 60% homologous to Shiga toxin 2 (Stx2). Stx2 is not neutralized by antibodies to either Stx1 or Shiga toxin produced by S. *dystenteriae* (1,3). The genes for Stx1 and Stx2 are encoded by temperate bacterio-phages. Shiga toxins 1 and 2 are AB_5 toxins where one A subunit is linked to five B subunits. These toxins are responsible for the disruption of protein synthesis, which can lead to cell death. In humans the B subunit binds to globotriaosylceramide, Gb3, which is expressed on renal tubular and vascular cells in the kidney, brain and in the Paneth cells in the intestine. The A subunit is an N-glycosidase. After binding and internalization of the toxin, the A subunit cleaves ribosomal RNA thus preventing transcription and overall protein synthesis (4). Breakdown of protein synthesis can result in cell death which in turn can lead to the damage and loss of function of tissues and organs.

Shiga toxins are not the only virulence factor of importance. STEC isolates of patients who suffer from HUS often carried the virulence gene *eaeA* which codes for intimin, a protein that enhances attachment and effacing of *E.coli* to intestinal epithelial cells by a type III secretion system (3).

The clinical symptoms of STEC infections include acute, sometimes bloody, diarrhea as well as more severe disease such as hemorrhagic colitis and hemolytic uremic syndrome (HUS) that can be fatal in up to 5% of cases (3). HUS is characterized by thrombocytopenia, hemolytic

anemia and renal failure. The time from exposure to onset diarrhea is around 4 days and the advancement to HUS from onset of diarrhea ranges from 1 to 10 days (4).

In the U.S., most documented STEC infections involve *E.coli* O157:H7, which results in 73,000 cases a year, and six non-O157 serogroups (O26, O45, O103, O111, O121 and O145) which account for the majority of non-O157 STEC infections (1). Even though O157:H7 STEC may dominate the headlines in the U.S., the CDC has estimated that non-O157 STEC infections may cause twice as many illnesses as *E.coli* O157. The large number of undiagnosed non-O157 STEC infections may be attributed to insufficient testing for non-O157 STEC. Worldwide non-O157 STEC illnesses are as common if not more common than O157 STEC illnesses. As recently as 2011 there was a large outbreak of STEC O104:H4 in Germany linked to the consumption of raw sprouts and secondary transmission (5).

Approximately 8% of all persons diagnosed with O157 STEC infections develop HUS, with children of the age of five and under at the greatest risk (1). To make matters worse the infectious dose of O157 STEC and O111 STEC is relatively low at <100 organisms (1). Although O157 STEC is closely associated with the development of HUS it is well documented that non O157 strains of STEC can lead to the development of HUS. Recent research suggests that Stx2 positive STEC isolates are 5 times more likely to cause severe disease than STEC isolates negative for Stx2 and that there is a positive association between the presence of Stx2 and the development of HUS (4). Thus, the best indicator of the potential for the development of HUS would be accurate detection of Stx2.

Health agencies such the CDC stress the importance of prompt and accurate diagnosis of STEC infections. Timely and appropriate treatments are needed to reduce renal damage and improve patient outcome. Prompt appropriate treatment is crucial because it is widely believed that the use of antibiotic therapy with O157 STEC infections can lead to more severe disease such as HUS due to increased toxin production (1).

Because rapid detection of STEC is key in preventing unnecessary treatment that may cause further severity of disease and renal damage it is recommended that use of enzyme immunoassays (EIA) be a standard practice along with culturing. In addition, prompt results of non-culture EIAs that test for the presence of Shiga toxins directly in stool samples can offer additional benefits such as having the ability to detect all serotypes of STEC (1, 2). Toxin different-iation assays provide an even greater diagnostic tool because of the positive association between Stx2 and the development of HUS.

The CDC recommends non-O157 STEC and O157 STEC testing for all stool specimens from patients with an acute onset of community-acquired diarrhea as well as all patients suspected of

having HUS (1). US studies have shown STEC were detected in 0%-4% of all stools submitted for testing at clinical laboratories. These rates are similar to those of *Salmonella* species, *Shigella* species and *Campylobacter* species (1).

In conclusion, STEC is a serious public health concern. With increases in epidemiologic knowledge and advancements in culturing technique and rapid enzyme immunoassays, we will be better able to provide more prompt and accurate diagnosis and treatment that may prevent further illness and unnecessary financial costs.

J. Heptinstall and A. Dandro

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