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RESEARCH NEWS

Outbreaks due to shiga toxin-producing E. coli continue to pose a serious health risk to individuals of all ages, especially children and the elderly. A recent outbreak due to a contaminated water supply in Walkerton, Ontario, Canada, served to highlight the gravity of the disease, as at least 7 deaths were reported to be associated with the illness. Approximately 30 children with shiga toxin producing E. coli were identified during the epidemic, 8 required dialysis and 1 child succumbed from hemolytic uremic syndrome. Synsorb, a synthetic Pk trisaccharide bound to silica beads, was used in the management of some of these children in a non-randomized fashion. The efficacy of Synsorb awaits completion of phase 3 studies. The following review describes two new exciting approaches which hold considerable promise for the treatment and prevention of the hemolytic uremic syndrome. It is hoped that in the near future, novel treatments such as those described here, will ameliorate the serious morbidity and mortality associated with outbreaks of shiga toxin-producing E. coli.

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Molecular Decoys: Novel Approaches to the Prevention of Hemolytic Uremic Syndrome

A review of: Kitov PI, Sadowski JM, Mulvey G, *et al*. 2000 Shiga-like toxins are neutralized by tailored multivalent carbohydrate ligands. Nature 403:669–72. Paton AW, Morona R, Paton JC 2000 A new biological agent for treatment of Shiga toxigenic Escherichia coli infections and dysentery in humans. Nature Medicine 6: 265–72.

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HEMOLYTIC UREMIC SYNDROME, the most common cause of acute renal failure in children, is almost always a sequela of gasteroenteritis due to shiga toxin-producing E. coli (STEC). Shiga toxins (Stx) bind to glycolipids, bearing a trisaccharide (known as Pk) on the gastrointestinal epithelial cell surface, and are internalized and transported to the cytosol where they inactivate the 28S ribosomal RNA. Protein synthesis is inhibited, the epithelial cell dies and hemorrhagic colitis often ensues.

From the gastrointestinal tract, tiny quantities of Stx gain access to the circulation. Renal endotheilal cells of young children are particularly susceptible to the toxin, presumably due to their high level production of Stx-receptors. Damage to the glomerular endothelium results in fibrin and platelet depostion, sludging of blood flow and shearing of red cells. Thus, decreased platelet count, hemolytic anemia and renal failure, the hallmarks of HUS, can be ascribed directly to the damaged renal endothelium.

While much is known about the pathophysiology of HUS, therapy remains sub-optimal and supportive, at best. Lack of an effective therapy for the infectious stage of STEC gastroenteritis led investigators to attempt to prevent the action of shiga toxin, once released. The first of these therapies utilizes a synthetic Pk trisaccharide linked to silica beads. Within the intestine, these beads should bind free toxin, preventing its access to the intestinal mucosa or systemic circulation. The compound, named Synsorb Pk, is currently being studied in phase III clinical trials.

Now, two new studies describe elegant and innovative methodologies that should enhance our options for prevention of HUS in children with STEC gastroenteritis. In the first of these Kitov *et al*. report a multivalent inhibitor for Stx that was synthesized through a chemical tour de force. The product, which they call STARFISH, consists of two Pk trisaccharides, linked to an adapter and multimerized

into a 5-armed ring that, indeed, resembles a starfish. They demonstrate that the in vitro inhibitory activity of STARFISH-Pk is orders of magnitude greater than the univalent trisaccharide and is by far the most active inhibitor of Stx yet identified. Crystallography demonstrated that the remarkable activity of the inhibitor results from the precise spacing of the starfish's arms and the ability to form 5 interactions with a single toxin molecule. STARFISH is water soluble, and therefore might be effective as a systemic therapy even after toxin has gained access to the circulation.

In the second report, Paton *et al*. describe an even more novel approach to inhibit the action of Stx. Rather than utilize synthetic sugars attached to an inorganic material, Paton *et al*. genetically engineered a harmless laboratory strain of E. coli to produce the Pk trisaccharide on its surface. Engineered bacteria were capable of binding large amounts of Stx and neutralizing its activity. Remarkably, Pk-recombinant bacteria administered orally to mice completely protected them from challenge with lethal doses of Stx-producing bacteria. This unique strategy raises the possibility that children may someday be intentionally colonized with protective bacteria in order to prevent the destructive effects of a pathogenic organism.

Outbreaks of STEC infection continue to occur with regularity. Prevention of the deaths that invariably occur during these outbreaks will require increased vigilance for the presence of STEC bacteria in food and water supplies, rapid diagnosis, and coordinated responses to epidemics. With the addition of the novel inhibitors of Stx described here, it is hoped that hemolytic uremic syndrome will become a rare and preventable disease.

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