

## Small Round Structured Viruses: An Important Infection Control Problem?

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Outbreaks of gastroenteritis and endemic cases of gastrointestinal infection are common important health problems among adults and children in the United States. Mortality is rare, but morbidity and economic losses are frequent. Much has been written about these infections in children and populations at risk, including daycare center attendees and their parents, sexually active gay men and institutionalized individuals in hospitals and chronic-care facilities. Nevertheless, the majority of cases of gastroenteritis in the United States are undiagnosed when careful evaluation is performed in research laboratories. Less than 20% of persons affected seek medical care, although it is known that over half alter their daily activities.<sup>1</sup> The impact of acute gastroenteritis on patients, employees and their relatives and friends is tremendous. The outbreak of gastroenteritis described by Gellert and colleagues in this issue of *Infection Control and Hospital Epidemiology*<sup>2</sup> illustrates many of the problems we face as healthcare professionals in defining, controlling and preventing these diseases.

Norwalk virus and the related small round structured viruses (SRSV) are a major cause of acute nonbacterial gastroenteritis in adults. These viruses occur in outbreak settings. They probably also occur endemically in the United States, although this has not been studied. SRSV are resistant to acid,<sup>3</sup> are not controlled by levels of chlorine used daily in the course of purifying municipal water supplies<sup>4</sup> and are highly infectious. Attack

rates in the range of 50% are reported for most outbreaks, such as this one. Water, ice and a wide range of foods, including baked goods, oysters, clams and salads have been implicated as vectors in these outbreaks. Secondary infection is usually reported. In the current outbreak, secondary infection occurred in 32% of ill convalescent center employees' family members and 53% of household contacts of employees in the affiliated hospital.<sup>2</sup> The incubation period of infections with SRSV is 24 to 48 hours, and symptoms last approximately the same amount of time. A median duration of symptoms of two days was described by Gellert, et al.<sup>2</sup> Viral shedding in the stool can occur up to four days after exposure, or one to two days after the onset of symptoms. Asymptomatic viral shedding has not been studied, but may occur.

By all criteria, the number of cases of gastroenteritis in adults caused by SRSV is underrepresented. Except for some Caliciviruses, SRSV have not been cultured, and no animal model of infection exists except in humans. Studies of these important agents have relied upon immune electron microscopy (IEM) and enzyme-linked immunosorbent assay (ELISA) techniques that use a small, limited amount of reagents obtained from humans exposed in outbreaks or volunteers in research studies. Worldwide, only a handful of research centers have the reagents necessary to perform these techniques. Because of the theoretical concern of passing retrovirus infections by giving stool filtrates obtained from outbreaks to volunteers (a process necessary for both safety testing and continued studies), evaluation of new SRSV likely will be limited in the future. Only Norwalk virus, Snow Mountain Agent, Hawaii Agent, Montgomery County Agent and "W" Agent have undergone studies in volunteers, and the study inoculums have a sufficient enough track record so that these studies can continue.

Many of these viruses are related antigenically as well as structurally. By radioimmunoassay

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(RIA), a serologic response to Norwalk virus was shown in paired sera from individuals with serologic evidence of infection with human Calicivirus UK2 and UK4.<sup>5</sup> A similar relationship has been shown between Snow Mountain Agent and Norwalk virus.<sup>6</sup> In cross-challenge studies in volunteers, Norwalk virus produced protective immunity in volunteers later challenged with Montgomery County Agent. However, it did not protect against Hawaii Agent.<sup>7</sup>

The purist may have doubts about concluding that an SRSV caused this outbreak, based on characteristic symptoms and IEM identification of SRSV in one of 30 stools. Given the difficulty of diagnosing these viruses, it is little wonder that the Centers for Disease Control (CDC) have established a definition of a characteristic outbreak. Detecting antigen and antibody by techniques using precious reagents can only be performed in special cases and selected outbreaks. While there are many outbreaks without cause that potentially could be investigated, only a few can be studied. This limitation tends to cause physicians to minimize the importance of these viruses, because in many outbreaks it is never proven whether or not SRSV are the cause.

IEM revolutionized our understanding of viruses as a cause of gastrointestinal infection two decades ago. We now need to apply new methods to increase further our understanding of these important infections. Cloning SRSV has proved difficult because of the small number of viral particles present in the stool. Norwalk virus just recently has been cloned, and it is hoped that this will enable further study of this ubiquitous agent.<sup>8</sup> Although previous attempts have been unsuccessful, methods to culture these viruses should follow. It is hoped that commercially available reagents eventually will be available, and further studies to compare shared antigens between these viruses can be performed. Our knowledge of SRSV has plateaued with the ability to describe outbreaks. We now need to proceed to the next step of understanding, and examine human immune response to infection, pathophysiology and occurrence of endemic illness.

New efforts may revolutionize our thinking about gastroenteritis in adults in the United States. In the future, it is hoped that rapid techniques can be developed that could be used to screen contaminated food and water. Specific foods at high risk, such as clams and oysters, may be candidates for periodic testing prior to marketing. Viral particles may also be detected in diseased tissues. This could help expand our understanding of the range of disease caused by these viruses. Frequent and recurrent infections with these viruses may be shown to occur. Death directly related

to infections in certain hosts may be proved, rather than speculated, as it is in the outbreak described.

Will this new knowledge help prevent non-bacterial gastroenteritis and its consequences? There is no doubt that it will contribute to prevention. A rapid test for SRSV in this outbreak, performed when the virus was first present in the acute-care hospital, could have resulted in quick infection control interventions that may have prevented the spread of the virus to the convalescent center. The fact that people do not usually report acute gastroenteritis to health authorities underscores both the ubiquity of this disease and the need for tests to detect infection early. Ultimately, it may be possible to produce a vaccine to protect against SRSV infection. To develop vaccines, a much better understanding of the host response to these viruses is required. Studies in U.S. volunteers have shown that serum antibody does not protect individuals against subsequent infection with Norwalk virus.<sup>9</sup> Levels of secretory IgA from duodenal secretions are similarly nonprotective.<sup>10</sup> Common viral antigens among these viruses need to be determined for successful vaccines to be developed.

Are common infection control practices adequate to prevent infection, or are we faced with endemic cases that occasionally spawn outbreaks such as the one described? The answers to these questions await better tools to study these viruses.

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