
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

# Clinical Microbiolog Newsletter

Vol. 6, No. 8 April 15, 1984

## Human Rotavirus Infection

Petrie Rainey, M.D., Ph.D.
Mary York, Ph.D.
*Microbiology Section, Clinical Laboratories*
*Department of Laboratory Medicine*
*University of California*
*San Francisco, California 94143*

A number of viruses have been associated with acute nonbacterial gastroenteritis including adenovirus, astrovirus, calicivirus, coronavirus, and minireovirus, but only Norwalk agent and rotavirus have been unequivocally implicated in human disease. The former is responsible for epidemic infections in school-age children and adults, whereas the latter is responsible for both endemic and epidemic disease. Rotavirus infects all ages, but is of greatest significance in children from 6 months to 2 years old (2). It has been suggested that rotavirus is responsible for up to 80% of viral gastroenteritis (13).

Initially, electron microscopy (EM) was used to detect rotavirus particles in diarrheal stools. Subsequently, a multitude of other techniques for detecting the virus have been developed, including immune EM, immunofluorescence, radioimmunoassay, RNA electrophoresis, and enzyme-linked immunosorbent assays (ELISA) (3,5–9, 13, 15, 18, 20, 21). The advent of commerical ELISA assays for rotavirus (Rotazyme, Abbott Laboratories, North Chicago, IL: Enzygnost, Behring Institut, Marburg, Federal Republic of Germany; Dako, distributed by Accurate Biochemicals, Huntington, NY) now allows the rapid diagnosis of rotavirus infection by clinical laboratories not having specialized equipment and technology available to them.

### Rotavirus

Rotavirus is a member of the reovirus family. The intact particle is 70 nm in diameter and has a double-shelled outer capsid, which causes the virus to resemble a wheel (Latin, *rota,* wheel). Both single- and double-shelled particles are seen in infected stool. The outer shell contains type-specific antigens, whereas the inner shell contains group-specific antigens (2, 21).

There are two major serotypes of human rotavirus and an unknown number of less common human serotypes (7, 20, 21). Four major groups of rotavirus have been identified, represented by human, bovine, porcine, and canine–simian strains (7).

The genome consists of 11 segments of double-stranded RNA. The patterns produced by electrophoresis of the RNA have led to the identification of multiple electropherotypes. Serotype appears to correlate with mobility of segments 10 and 11, whereas segment 6 is associated with group-specific antigen. It has been suggested that rotavirus may undergo genome reassortment similar to that seen with influenza viruses (6). Further work is required to clarify the significance of the electropherotypes.

Attempts at propagating human rotavirus in cell culture have had little success (13). Some animal strains, however, are readily cultured. Antibodies to these strains cross-react with human rotavirus and were used to develop the current immunoassays.

### Rotavirus Gastroenteritis

Rotavirus has been implicated in about 50% of the cases of acute diarrhea in hospitalized children between 6 months and 2 years of age (2, 12). Infection occurs worldwide and peaks in the winter months in temperate climates. Primary symptoms are vomiting and/or diarrhea. Vomiting and dehydration are more marked in rota-

### In This Issue



0196-4399/84/$0.00 + 02.00

virus infection than in other infant diarrhea. Therapy is limited to fluid and electrolyte replacement. The disease generally resolves spontaneously in 4 to 8 days (2). An upper respiratory prodrome is common in children with rotavirus disease (12, 13), and rotavirus has occasionally been demonstrated in upper respiratory tract specimens (19). Rotavirus has been detected in the stools of some cases of sudden infant death syndrome, but the significance of this is unclear (19).

By 2 years of age, most children have antibody to both major rotavirus serotypes (2). Antibody is not associated with resistance to infection, but moderates the severity of symptoms. This reduction in disease severity appears to be serotype-specific and may be mediated more by intestinal IgA than serum IgG (1, 20).

Rotavirus infection is not uncommon in older children and adults, but disease is generally mild or asymptomatic (2, 13, 16). Severe gastroenteritis is uncommon and usually occurs during epidemics (5, 16). Whether an uncommon serotype is responsible for such epidemics has not been investigated. Elderly (4) and immunosuppressed (17) patients may have more severe symptoms with rotavirus infections.

Although children less than 6 months old are frequently asymptomatic (for reasons that are not clear), they are readily infected with and shed virus (1, 2, 13, 14). In some nurseries where the virus had become endemic, about 50% of the infants had rotavirus in their stools. Of these, about three-fourths were without symptoms (1, 14).

Asymptomatic viral shedding can occur in all age groups. In one day care center, 12% of children under 2 years of age had rotavirus positive stools but no symptoms (10). As many as 1% of asymptomatic adults may shed rotavirus (16).

## Laboratory Diagnosis

Detection of rotavirus in stool by electron microscopy was the original method of diagnosis and remains a reference method. Because of the distinctive appearance of the virion, false positive results are minimal when the test is performed by an experienced microscopist. However, detection by EM generally requires virus concentrations on the order of $10^7$ to $10^8$ particles per ml (15). Many methods for detecting rotavirus, including EM, are not practical for most laboratories. However, the commercially available ELISA assays can be readily performed.

Rotazyme is presently the only rotavirus test manufactured in the United States for clinical use, although other commercial test kits should be available shortly. The test is carried out by incubating a stool sample with a plastic bead to which guinea pig antibody to simian rotavirus SA-11 has been adsorbed. After a washing step, any virions bound to the bead react with added rabbit antirotavirus antibody which has been conjugated with horseradish peroxidase. The amount of peroxidase bound to the bead is measured by the change in optical density after incubation with o-phenylenediamine. This change may be measured visually or with a spectrophotometer and reflects the concentration of rotavirus in the stool sample.

In serial dilution studies the Rotazyme assay was more sensitive than electron microscopy; the limit of detection was at least tenfold fewer virions per ml than for conventional EM (9, 15). The results of several clinical studies suggest 90 to 95% sensitivity for Rotazyme (3, 8, 9, 15, 18).

Overall the test has a 90 to 95% specificity (3, 8, 9, 15, 18), but Krause et al. reported a high incidence of false positive results in infants less than 3 months old. When stools from an unselected series of infants (most of whom did not have diarrhea) were screened, 22% were positive and greater than 90% of these were falsely positive as determined by failure to detect rotavirus by EM and by demonstrating reactivity with serum from nonimmunized animals (11). False positive tests do not appear to be a problem in children over 3 months of age or in adults.

Enzygnost and Dako are ELISA assays that use antibody-coated microtiter trays instead of plastic beads and are designed for multiple sample testing. These assays have the advantage that they include nonimmune serum control wells to enable differentiation of false and true positives in neonates. Neither Enzygnost nor Dako have had extensive published evaluations. However, in one study, no significant differences were seen in the sensitivity and specificity of Enzygnost and Rotazyme (18).

The ELISA rotavirus tests appear to be most useful for diagnosing gastroenteritis in children 6 months to 2 years old, and in epidemiology studies. A positive test should not preclude the search for other pathogens, because of the relative frequency of asymptomatic shedding of rotavirus. In children less than 3 months old, positive tests should be confirmed by EM or by an immunologic assay with controls for nonspecific interactions.

*References*


1. **Bishop, R. F. et al.** 1983. Clinical immunity after neonatal rotavirus infection. N. Engl. J. Med. **309**:72–76.
2. **Blacklow, N. R., and G. Cukor.** 1981. Viral gastroenteritis. N. Engl. J. Med. **304**:397–406.
4. **Cubitt, W. D., and H. Holzel.** 1980. Hospital acquired rotavirus infection in adults: who is at risk? J. Hosp. Infect. **1**:327–331.
3. **Cheung, E. Y. et al.** 1982. Comparison of Rotazyme and direct electron microscopy for detection of rotavirus in human stools. J. Clin. Microbiol. **16**:562–563.
5. **Echeverria, P. et al.** 1983. Rotavirus as a cause of severe gastroenteritis in adults. J. Clin. Microbiol. **18**: 663–667.
6. **Flores, J. et al.** 1982. Genetic relatedness among human rotaviruses as determined by RNA hybridization. Infect. Immun. **37**:648–655.
7. **Gaul, S. K. et al.** 1982. Antigenic relationships among some animal rotaviruses: virus neutralization in vitro and cross-protection in piglets. J. Clin. Microbiol. **16**:495–503.
8. **Hammond, G. W. et al.** 1982. Comparison of direct and indirect enzyme immunoassays with direct ultracentrifugation before electron microscopy for detection of rotaviruses. J. Clin. Microbiol. **16**:53–59.
9. **Keswick, B. H. et al.** 1983. Evalua-

tion of a commercial enzyme immunoassay kit for rotavirus detection. Diagn. Microbiol. Infect. Dis. **1:** 111–115.

10. **Keswick, B. H. et al.** 1983. Prevalence of rotavirus in children in day care centers. J. Pediatr. **103:**85–86.
11. **Krause, P. J. et al.** 1983. Unreliability of Rotazyme ELISA test in neonates. J. Pediatr. **103:**259–262.
12. **Lewis, H. M. et al.** 1979. A year's experience of the rotavirus syndrome and its association with respiratory illness. Arch. Dis. Child. **54:**339–346.
13. **Madely, C. R.** 1983. Viruses and diarrhoea: problems of proving causation, pp. 81–109. *In* L. M. de la Maza and E. M. Peterson (eds.), Medical virology II. Elsevier Biomedical, New York.
14. **Murphy, A. M., M. B. Albrey, and E. B. Crewe.** 1977. Rotavirus infections of neonates. Lancet **2:**1149–1150.
15. **Rubenstein, A. S., and M. F. Miller.** 1982. Comparison of enzyme immunoassay with electron microscopic procedures for detecting rotavirus. J. Clin. Microbiol. **15:**938–944.
16. **Wenman, W. M. et al.** 1979. Rotavirus infection in adults. N. Engl. J. Med. **301:**303–306.
17. **Yolken, R. H. et al.** 1982. Infectious gastroenteritis in bone marrow transplant recipients. N. Engl. J. Med. **306:**1009–1012.
18. **Yolken, R. H., and F. J. Leister.** 1981. Evaluation of enzyme immunoassays for the detection of human rotavirus. J. Infect. Dis. **144:**379.
19. **Yolken, R., and M. Murphy.** 1982. Sudden infant death syndrome associated with rotavirus infection. J. Med. Virol. **10:**291–296.
20. **Yolken, R. H. et al.** 1978. Epidemiology of human rotavirus types 1 and 2 as studied by enzyme-linked immunosorbent assay. N. Engl. J. Med. **299:**1156–1161.
21. **Zissis, G. et al.** 1981. Human rotavirus serotypes. Lancet **1:**944–945.

## Editorial

# The Impact of DRGs on Hospital Laboratories

John M. Miller
*Assistant Director for Laboratories*
*University of Chicago Medical Center*
*Chicago, Illinois 60637*

Under the Medicare prospective payment system (PPS), hospital reimbursement is based on various Diagnosis Related Groups (DRGs). DRGs were developed by Professors J. D. Thompson and Robert B. Fitter at Yale University in the late 1970s. They described a patient classification scheme for utilization review. The passage of the Tax Equity and Fiscal Responsibility Act of 1982 (TEFRA) was the nation's first real introduction to DRGs, a classification scheme used to adjust the cost per case for all Medicare patients requiring hospitalization. DRGs represent a unit of payment and in a positive sense, hospitals will now be paid according to what's wrong with the patient. Although you won't see any immediate direct effect, pressure put on your hospital by this system will eventually filter down to and impact on the laboratory. The new system is designed to decrease the cost of health care: hospitals that can lower their operating costs will do well, those that don't prepare for DRGs will be in trouble. In this article, I'll briefly discuss how factors such as "creative" staffing, improving test utilization, cost-effective purchasing, and even in-hospital public relations will allow the laboratory to survive under the DRG system.

The basic premise of PPS is to provide an incentive to the hospital to shorten the patient's length of stay (LOS). In most cases payment will be based on the DRG used and not on the time the patient spends in the hospital; therefore, shortening the LOS will decrease costs and increase revenues. As far as the laboratory is concerned, testing will be more intensive early in the patient stay, and may even begin before admission. Preadmission testing, along with more emphasis on an earlier, faster turn-around time (TAT), will permit earlier completion of diagnostic procedures and a more accurate determination of the appropriate DRG. These changes will clearly stress the laboratories' ability to coordinate and manage this information flow from both inpatient and outpatient sources. We may elect not to perform certain types of tests because of a long TAT. As is customary in many laboratories, we may not be able to "batch" low volume tests and run them only once a week because of pressures to make the test results available earlier during the patient's stay. You will hear statements such as "don't let the late laboratory result force us to keep the patient an extra day." We will increase the number of special arrangements with groups of physicians to tailor our services to their particular needs. For example, in the newborn nursery, blood for bilirubin assays will be drawn earlier in the day so the laboratory can get the results back early and allow for a midday discharge. In order to handle weekend admissions, we will need to have more services available routinely on weekends as well as evenings and nights when traditionally only stat procedures are offered. A patient arriving at 3 p.m. will need to have tests completed by that evening. To accomplish this, our staff scheduling skills will need fine tuning.

Another possible way to speed the diagnostic process is to allow the laboratory director to order additional tests as indicated without costly and time-consuming interactions with the clinician. The laboratory director, in consultation with clinicians, will be given increasing authority to set up and manage testing protocols.

An obvious effect of DRGs on hospitals will be pressure to hold down costs. Since labor is the most expensive component of providing laboratory services, we can expect demands to cut our staff. Labor reductions are usually best accomplished through attrition and increased automation. But there are other ways to save salary

© 1984 by Elsevier Science Publishing Co., Inc.
0196-4399/84/$0.00 + 02.00