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Viral Enteritis

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Twenty years ago, even the most sophisticated diagnostic facilities could identify a cause of acute diarrhea in only 20 per cent or less of all cases in childhood. Now that figure approaches 80 per cent.[38] By far the most important factor contributing to this remarkable improvement in diagnostic success is the recognition of human rotavirus as the major cause of acute diarrhea in young children. Other viral and bacterial enteric pathogens in man have been identified during these two decades and our understanding of the mechanisms by which some infections cause diarrhea has improved greatly.[24] This new knowledge has provided a sound basis for impressive advances in active therapy and promising approaches to prevention of a problem that annually kills nearly 5 million young children in Africa, Latin America, and Asia (excluding China).[33] This article, which reviews current concepts of mechanisms and management of viral enteritis, will focus on rotavirus diarrhea and relevant experimental models.

The risk in making general comments on a subject with the global impact of the viral enteritides should be acknowledged. Certainly major regional differences exist in the manifestations and implications of these illnesses, based on a host of genetic and environmental factors that are most striking when developed and developing countries are compared. The author's direct exposure to the problem has occurred primarily in the former environment. Furthermore, this article places emphasis on pathophysiologic events reflecting the author's background, rather than the relative importance of major contributions made to this field by a range of disciplines, including virology, veterinary medicine, epidemiology, and public health. Whatever the perspective from which the recent history of viral enteritis is viewed, an exciting, fascinating story is revealed.

CAUSES OF VIRAL DIARRHEA

It is reassuring to note that in days gone by, the wise clinician who said, when confronted with a young child with acute watery diarrhea, "it's

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Table 1. *Probable Human Enteric Viral Pathogens*

Human Rotavirus*
Small Round Viruses (SRV)
a) Structured
Norwalk*
Taunton
Morin County
Snow Mountain
Astrovirus
Enteric calici virus
b) Featureless
Cockle
Wollan
Ditchling
Enteric Adenoviruses
Coronaviruses

*Strong evidence supporting pathogenicity.

a virus" was correct—usually! Actually the same can be said for our colleagues in veterinary medicine, who deal with a devastating global problem of "scours" in young farm animals.[39, 45] In the case of a young child, the usual viral pathogen is rotavirus, but several other viruses listed in Table 1 are known to be capable of causing diarrhea.

Because many of these agents have not been characterized completely, some uncertainty and disagreement continue over their nomenclature. One hopes that the terminology that follows is in keeping with a consensus view.

Rotavirus

These RNA viruses of distinct structure are the most important and best characterized of the human viral pathogens.[27] Rotavirus particles consist of outer and inner capsids, surrounding a central core containing nucleic acid. Perhaps it is because of their apparent preference for differentiated villus enterocytes and the dome epithelium overlying Peyer's patches that these viruses have been difficult to adapt to cell culture. In infected cells, viral particles appear first in finely granular cytoplasmic areas and later in distended cisternae of the endoplasmic reticulum. Probably, there are 11 segments of double stranded RNA in the rotavirus genome.

Little is known about cell surface receptors for rotaviruses, but specificity seems directed more at cell type than at species.[49] They infect the villus epithelium of the small intestine, not other regions of the gut, and not other organs such as the respiratory or urinary tract. Human strains have been grown in calves, piglets, and other animals; obviously comparable experiments have not been conducted in man, but it is unlikely that a reservoir of human pathogens will be found in the animal kingdom.

Four distinct serotypes of human rotavirus are based on viral neutralization tests[18]; two of these do occur in animals. Serotypes 1 and 3 have emerged as the most frequently identified agents in human cases but the relationships between virulence, host resistance, geographical distribution, and serotype are not clear. Rotavirus serum antibodies can be detected in 90 per cent of 2-year-olds studied in different parts of the world. The extent

to which this immune response is protective is not known, but sequential infections with different strains occur in the same child. Also, children with combined immune deficiency can experience serious difficulties in shedding the virus.[13]

These agents were reported first in 1973 by Ruth Bishop and her Melbourne colleagues who showed a duodenal lesion associated with viral invasion of the intestinal epithelium[4] and massive fecal excretion of virus during acute disease but not during convalescence.[3] Shortly after, infection of a human volunteer, and immune fluorescent studies showing diffuse involvement of the upper intestinal villus epithelium were reported.[41] Most other studies have found a close relationship between rotavirus excretion and acute diarrhea in infants. However, reports from France in which significant numbers of asymptomatic children were shown to excrete virus in their stools[11] and from Perth, Australia, question the diagnostic meaning of rotavirus sightings in stools of certain populations.[7] Another intriguing observation, made in several centers but not yet fully explained, is fecal excretion of rotavirus particles by asymptomatic newborn infants.[5, 12]

Spread of human rotavirus enteritis is human-to-human and presumably fecal-oral.[5] The hardiness of the virus is impressive, in that it retains virulence long after shedding, as evidenced by its apparent capacity to induce nosocomial infections after long periods on hospital furniture, walls, and floors. In the community, at least in temperate climates, the winter seasonal incidence is striking but unexplained.

Small Round Viruses (SRV)

(a) ***Norwalk virus.*** Identified after an outbreak in Norwalk, Ohio, this virus is the best characterized of the SRV observed in acute diarrheal stools.[17, 29] Proof that the Norwalk agent is pathogenic in man comes from its identification in epidemic diarrheal stools, documented serological responses to acute infection, and transmission to human volunteers. A small 27nm particle, the virion contains a simple structural protein of 62,000 daltons; its nucleic acid content is not known. Like the rotavirus, Norwalk agent seems to invade the upper intestinal mucosa, causing histologic lesions in infected volunteers.[51] However, these tiny particles have not been identified in duodenal tissue from these volunteers.

(b) ***Other SRV.*** A large group of viruses share certain features attributed to Norwalk agent. Morphologically they have been classified into featureless and structured groups (see Table 1). The association between gastroenteritis and the structured group is better supported than for the featureless group.[9] In fact, except for the Norwalk agent, hard evidence to confirm the pathogenicity of these viruses is tenuous.

All SRV are similar in size and, when it has been assessed, in their buoyant density. All have been observed in stools during acute diarrheal illness, usually in the course of an epidemic but in less quantity than rotaviruses.

Calicivirus has a distinctive 6-pointed star structure, and astrovirus, a 5- or 6-pointed star on the surface.[35] These latter two members of the group are the only ones that have been propagated in cell culture to date. The biochemical and genetic characterization of the SRV remains very incomplete.

Enteric Adenoviruses

These agents have been associated with gastroenteritis in children for years but the suggestion of a strong relationship arises from recent electronmicroscopic studies of stools.[36] Similar in size to rotavirus, adenoviruses have a distinct icosahedral morphology. Radioimmunoassay and enzyme immunoassay systems have helped in identifying these infections.[1] Adenoviruses may be common causes of acute diarrhea, as claimed by some, but they are identified in up to 8 per cent of all stools, including those of asymptomatic controls.

Coronaviruses

These pleomorphic, enveloped RNA viruses possess a characteristic fringe of radiating projections.[10] Human strains have been propagated in fetal intestinal organ culture, but not in cell culture. Long recognized as a cause of acute diarrhea in animals (for example, transmissible gastroenteritis in piglets) they have been identified now in patients with diarrhea in many regions of the world. Definitive studies to establish their pathogenicity are lacking still.

CLINICAL FEATURES

Rotavirus

The pattern of symptoms experienced by a young child in response to a first exposure to human rotavirus is rather consistent.[5, 15, 16, 53] Severity of those symptoms and their impact on the child vary greatly depending on many variables, including the extent of the intestinal lesion, the resistance, and the reserves of the host.

Within two days of exposure there is low grade fever, anorexia, and usually vomiting lasting up to 48 hours. Watery diarrhea and cramps begin by the second day, and last for up to 6 days. Fecal output can be massive causing rapid, even fatal dehydration, and acid-base dysequilibrium. Physical signs of dehydration, loss of body weight, decreased skin turgor, sunken fontanelle and eyes may develop before one is aware of diarrhea, because watery stool may pool in the bowel lumen or it may be confused with urine in the diaper.

During the acute phase of this illness, auscultation of the abdomen reveals hyperactive bowel sounds. Where severity is difficult to evaluate, rectal examination is particularly helpful, providing an instantaneous assessment of consistency and amount of stool. Examination of those feces usually reveals little if any blood or cellular exudate, but there may be reducing substance. Typically, the disease follows a self-limited course of 4 to 10 days with diarrhea settling by the sixth day or sooner, and subsequently a gradual return to normal appetite and activity.

Laboratory data from severely affected patients show a raised fecal Na^+ concentration with isotonic dehydration and reduced plasma bicarbonate levels. The severely affected child, particularly an infant, may develop lethal hypernatremia or hyponatremia with marked acidosis. If the child

has been receiving hyperosmolar drinks (commercial beverages, gelatin water, fruit juices undiluted) or solutions of very high salt content (certain commercially prepared soups, milk that has been boiled for an extended time), the likelihood of hypernatremia is increased.[56] Standard hematologic indices may be distorted by dehydration and in some cases serum transaminase activity is increased slightly.

Electron microscopic identification of virus in stools during acute diarrhea is still an effective diagnostic technique. Enzyme-linked immunoassays (ELISA) and reverse passive hemagglutination techniques have been developed as sensitive relatively inexpensive alternatives.[57] Of course none of these techniques distinguishes between different serotypes and species of the virus. In most cases, but not all, a rising serum antibody titer to rotavirus can be measured after an acute attack.

Although it is the infant who is most vulnerable to this disease, symptoms in the *newborn infant* can be very mild or absent in the presence of fecal virus excretion.[5, 15, 16, 54] In one study only 28 per cent of newborn babies excreting the virus had diarrhea. These observations are not explained completely by a protective effect of maternal milk feeding, having been observed in nonbreast fed babies; in a controlled trial supplementation of oral feedings with human gamma globulin protected young infants from infection and disease.[2]

In *adults* rotavirus rarely causes severe diarrhea and usually symptoms are less severe than in children,[5] presumably because almost all have previously developed an immune response to the infection. This impression is gained from studies of family contacts of young patients,[53] and from experience with resident physicians newly arrived in a children's hospital. Nausea, anorexia, and cramps persist for 2 or 3 days but diarrhea is infrequent and brief. The elderly may have more severe symptoms than young adults judging from very limited observations on elderly relatives of affected infants. However, the aged are unlikely to come into close contact with infected babies frequently.

Norwalk and Norwalk-like Agents

The clinical features of these infections, more common in adults than in children, have been documented carefully in adult volunteers.[28] Malaise, fever, nausea, and abdominal cramps are followed within 24 hours by vomiting, which is a prominent feature. Diarrhea occurs but not in all cases. During the Norwalk epidemic, 84 per cent of affected individuals suffered significant vomiting and only 44 per cent had diarrhea. Rarely do these infections cause significant dehydration. Stools are watery but they contain neither leukocytes nor blood. The clinical features of this group of infections seem to be indistinguishable, one from the other, but they appear not to be major pathogens in young children.

Viral excretion in stool is detectable from the onset of symptoms for about 72 hours. Techniques used to identify virus include electron microscopy, immuno-electron microscopy, and for the Norwalk virus, radioimmunoassay or an immune adherence hemagglutination assay.

Other Viruses

The relationship between other viruses and gastrointestinal symptoms is tenuous and does not allow for an authoritative description of associated

clinical manifestations at this point. Clinically significant diarrhea has been attributed to adenovirus, but an association between these agents and intussusception reported earlier has not been substantiated; crampy pain has been a prominent clinical feature.[36] When other viruses have been isolated from stool in association with epidemics of diarrhea, symptoms have been relatively mild; usually watery diarrhea, cramps, and vomiting are confined to less than 48 hours.

PATHOGENESIS OF VIRAL DIARRHEA

Rotaviruses invade the epithelium of the small intestinal mucosa,[3, 41] involving the proximal portion but extending diffusely to involve as much as the entire small bowel. Studies in rabbits show early and heavy invasion of Peyer's patch regions by rotavirus, suggesting a possible preferred portal of entry there.[22] There is extensive villus epithelial, not crypt epithelial invasion, and no infection of the stomach or colon. In animal studies, invasion of the surface epithelium of the small intestine generates a proliferative response in the crypts with a marked increase in the epithelial renewal rate.[14] As a consequence, the virus is shed but the epithelium becomes dominated by cells that have migrated quickly from the crypts and failed to undergo a normal process of differentiation. Diarrhea seems to be a result, not of direct viral damage, but of this subsequent poorly differentiated status of the bowel lining.[24] There may or may not be a structural lesion with shortened villi and reduced surface area which, when present, undoubtedly contributes to the functional compromise.

The Norwalk agent has not been identified in the mucosa but it causes a lesion in the upper intestine similar to that seen in rotavirus disease[51]; presumably for viruses of this group that are true pathogens, the interaction with the mucosa is similar. In the case of the other candidate viral pathogens, invasion of the mucosa of the gut has not been established.

Our current understanding of the mechanism of viral diarrhea is based mainly on studies of a corona virus enteritis of piglets, transmissible gastroenteritis (TGE).[24] This reproducible illness is identical to that produced in piglets by HRV. Although the two viruses differ, their interactions with the small intestine seem to be identical. At the height of TGE diarrhea, several functional abnormalities have been identified, each of which could contribute to excessive fecal salt and water losses. Brush border membrane disaccharidase activities are decreased as is the function of the basolateral membrane Na pump, the Na-K-ATPase system. The dominant transport defect appears to be a marked reduction in Na gradient-dependent glucose absorption across the intestinal brush border, but neutral NaCl absorption at this site is decreased also.[34] Absence of a functional high affinity brush border membrane glucose carrier seems to contribute to this diminished Na-facilitated glucose absorption.[29] It is of interest that alanine-Na cotransport may be only partially impaired in this acute viral diarrhea.[47, 48] Furthermore, there is no evidence of intracellular accumulation of cyclic AMP or GMP and no evidence of an active secretory process, such as one would encounter in cholera.[34]

We believe that this functional profile of the small intestine in acute TGE diarrhea, which is in keeping with current concepts of the profile of normal intestinal crypt cell function, applies to rotavirus enteritis. In TGE enteritis, virus has been shed from the mucosa by the time diarrhea becomes severe; this relationship may not apply fully to rotavirus disease in that rotavirus continues to be shed in stools during acute diarrhea.

In fed patients rotavirus and TGE stools contain concentrations of Na and Cl (45 to 55 mg per L) that are higher than normal but much less than those seen in secretory states like cholera.[53] These findings are compatible with the functional defects just described.

REPAIR OF THE GUT AFTER VIRAL INJURY

Recovery depends on several of the processes described above.[24] The rapid turnover of the epithelium combined with the peristalsic activity act to clear these superficial infections from the gut. The relative importance to this process of increased mucin secretions and immune globulins is not known.

Recovery of the epithelium is a matter not only of replacement of shed cells but also restoration of a functioning differentiated epithelium. In a well-nourished host this repair process usually is complete in 4 to 5 days. Probably regulation of cell proliferation in the crypts and the migration of the cells onto the villi is somewhat distinct from the factors controlling differentiation of these cells as they migrate. A range of hormones and neuropharmacologic factors influence these processes, but their direct relevance to clinical issues in not yet elucidated.

Not only may chronic undernutrition in the host alter susceptibility and shedding of the virus,[49] malnutrition also can be expected to alter these intestinal repair processes. Much is to be learned about chronic protein-calorie undernutrition, which in many clinical and animal models reduces the activity of cell proliferation in the gut. In animals, postnatal development and functional repair after acute experimental viral enteritis have been shown to be delayed.[8, 20] The role that micronutrients might play in these observations is not yet known, but it seems that nutritional depletion must be relatively severe before a significant effect on repair of the intestinal epithelium is noted.[21]

TREATMENT

Prevention

Some effective preventative measures have always been available. The proof that these diseases really are contagious merely reaffirms the crucial importance of breast feeding, and of hygienic measures in reducing incidence and severity. Available evidence supports the view that breast feeding reduces the incidence and severity of acute infantile diarrhea.[32, 33] The mechanism for this protective influence is not clear; rotavirus antibody is

found in human milk[52] and these IgA antibodies, linked to secretory piece, can be expected to resist intraluminal proteolysis.

Because spread of these infections is fecal-oral, personal hygiene, water supplies, sewage control, and food preparation are potentially important considerations. Rotavirus-infected subjects generously contaminate their environment, providing a potent source of oral contamination. Shell fish have been shown to harbor Norwalk virus, causing epidemics of acute vomiting and diarrhea. Of particular importance in pediatrics is nosocomical spread of rotavirus in particular, but other enteric viruses too.[42] These agents appear to be extremely hardy, so rigorous hygiene and careful cleaning of institutional furniture and equipment is an important preventive measure if children must be admitted to hospital. The high likelihood (> 30 per cent) of an infant developing viral enteritis when admitted to a modern hospital, particularly in the winter, is another reason to avoid such admissions if possible.

The preparation of effective, safe vaccines is hampered by the fact that these agents cannot be reliably propagated in tissue culture. Therefore, the rapid emergence of two groups of rotavirus vaccines now being subjected to clinical testing is remarkable. These vaccines are attenuated live virus preparations, one a calf virus, the others, Simian viruses.[33] Early controlled field trials of bovine strain RIT4237 vaccine to Finnish children showed a protective effect,[55] but subsequent ongoing large scale trials in developing regions have been less conclusive. Intense research attention is focused now on the Simian strains that in some trials have caused a febrile response on the third or fourth day after vaccination. High rates of infection and significant protection have been shown in limited trials of Simian viruses.[46] At present, no vaccine of proven safety and efficacy is available, but significant progress is being made toward that objective.

Active Treatment

Fluid and Electrolyte. The application of modern pathophysiologic principles to the fluid therapy of diarrhea has been one of the important medical advances of the century. Oral fluid therapy, stimulated in the early days by elucidation of the mechanisms for cholera-induced secretion, has had a dramatic impact on survival and morbidity from diarrheal disease.[23, 26, 37] A glucose-electrolyte solution, prepared for oral rehydration therapy (ORT) and promoted by the WHO Diarrheal Disease Program and by UNICEF since 1971, has been shown to be effective in rehydrating 90 to 95 per cent of cases of diarrheal dehydration, many of which might otherwise have needed intravenous fluids. For the child with a secretory bacterial toxin-induced diarrhea (for example, *Escherichia coli*, cholera), this solution theoretically promotes absorption of glucose facilitated Na absorption to compensate for secretory losses. For the child with viral diarrhea, it provides a balanced (equimolar glucose and Na) mixture of ions in an isotonic solution to make the best possible use of any absorptive capacity remaining in the sick intestine. It is important to recognize that this solution will not lessen diarrhea directly nor does it provide significant nutrition to the child. It maintains fluid balance, in most cases, for the brief period of a transient disease. For rare cases of viral diarrhea in which the entire length of small

intestine is involved, oral fluids may be insufficient and intravenous fluids may be required, particularly in the very young patient with little functional reserve.

Because oral fluid therapy is effective and safe and premixed cachets are cheap and easy to distribute widely, this measure alone has had a striking impact. In a Luanda, Angola, pediatric hospital, a decrease of diarrhea deaths of 98 per cent was observed in 1981; in many centers reductions of 40 to 50 per cent have occurred.[40] In developed countries, partly because of relatively easy access to intravenous fluids, partly because of the fact that the problem is less devastating, but also because of entrenched patterns of care and a slow response from commercial suppliers, oral rehydration therapy use has lagged behind that in developing countries. However, economic arguments, the documented ease and safety of the technique, and time are slowly winning the day.

Discussion continues to focus on the ideal formulation of oral rehydration therapy. The WHO formulation undoubtedly is effective, safe, and the best available solution for use in developing regions where very severe disease and nutritional depletion are prevalent. Reduction of sodium and chloride concentration to approximately half the WHO concentration (90 mM per L) seemed not to alter efficacy when the solution was studied in an American trial.[50] In fact, WHO recommends feeding equal volumes of water with oral rehydration solution (ORS) in treating young babies, and many commercial products distributed in developed countries are constituted with a Na concentration between 40 and 60 mEq per L similar to that of stools during acute viral diarrhea.

Several modifications of ORS are being considered based on recent pathophysiologic studies and clinical trials.[37] Amino acid, at least alanine, further enhances Na absorption in the presence of glucose. Because Na cotransport may be partially preserved in acute viral diarrhea, one approach is to supplement ORS with amino acid. After early promise, recent evaluation of glycine supplementation have not shown significant benefit; other amino acids and dipeptides are being assessed. More encouraging has been the use of oral rehydration solutions based on cooked indigenous foods. A rice base ORS used initially in an effort to develop a cheap available product has been shown to reduce stool output in acute diarrhea.[43] The mechanism for this response may relate to the content of amino acids and peptides in these mixtures. The availability of a solution that actually reduces stool volume has attractions beyond the obvious direct impact on the patient's fluid balance, because such solutions would gain much more enthusiastic acceptance than those currently available, which do not reduce diarrhea. It should be remembered that these improved ORS mixtures do not contribute significantly to the patient's nutrient intake.

Nutritional Treatment. Current trends to encourage early feeding of patients are supported by recently acquired pathogenetic data. The renewal and differentiation of the small intestinal epithelium, so crucial to the development and recovery of viral diarrhea, is very vulnerable to protein-calorie malnutrition, particularly in the young. Epidemiologic data from Pakistan indicate the average duration of symptoms is relatively extended among malnourished patients.[6] Earlier limited clinical trials show no

deleterious impact on diarrhea and improved nutritional status in children fed early in the course of infectious diarrhea.[24] More extensive studies of this question are in progress. The more marginal the patient's nutritional status at the onset of enteric infection, the more important early feeding becomes.

Concerns have been expressed that early ingestion of dietary protein may predispose the patient to allergic reactions in the gut. Theoretically, antigen entry across the infected mucosa could be enhanced, triggering a hypersensitivity reaction in the gut; in the view of some clinicians this sequence of events does occur with milk feeding. Our data on intact protein transport during acute experimental viral enteritis showed, in vitro, increased absorption only during the early invasive phase of the viral infection, but in vivo studies of intact animals did show enhanced protein uptake during viral diarrhea.[31, 32] In a recent study by Heyman and associates using a germ-free mouse model, protein absorption was enhanced early in rotavirus infection, but the introduction of enteric bacteria greatly increased intact protein absorption.[25] The immunologic significance of this observation is uncertain and studies of early feeding have not shown an increased occurrence of sensitivity reactions.

Another consideration in the nutritional management of viral enteritis is the capacity of the infected intestine to deal with dietary disaccharides, particularly lactose. Although in clinical and experimental studies, lactase activity is significantly diminished, it is relatively rare to encounter lactose intolerance during convalescence. The exception seems to be among some aboriginal people, where lactose is poorly tolerated even in health, but especially in the face of small intestinal disease.

Drugs. No pharmacologic agent has been shown to have a place in the treatment of acute viral diarrhea.[19] Efforts continue in the search for drugs that may reverse the mechanisms contributing to the transport defects described above, and influence the process of cell differentiation so central to these processes. Agents that enhance absorption in vitro have been either ineffective or toxic in vivo. Antidiarrheal drugs that continue to be promoted for use in young children do not alter fecal volume significantly. By altering peristalsis and at times appearing to change output, they are potentially hazardous.

SUMMARY

Rotavirus has emerged as the major enteric pathogen causing acute diarrhea in young children throughout the world. Other viral pathogens have been recognized and additional candidate agents are suspected but none approaches rotavirus in its global impact. A strong appropriate emphasis has been placed on preventive therapy. Although vaccines are not yet available, it is clear that improved hygienic practices, particularly in pediatric institutions, and breast feeding can do much to prevent serious illness during the early months when babies are so vulnerable. During the past decade, from clinical studies and animal models, much has been learned about the pathogenesis of rotavirus diarrhea. These findings provide

a sound basis for the use of rational oral fluid therapy, early feeding, and avoidance of drugs during active management. Among the many challenges that remain are the elucidation of the full spectrum of enteric viral pathogens, their impact on man, and their prevention and active therapy.

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