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Pediatric Cholera: Pathophysiology and Treatment

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Introduction

HOLERA is an acute intralumenal intestinal disease caused by *Vibrio cholerae*. The etiological agent is a gram-negative, curved, rod-shaped bacterium which is actively motile, with a single polar flagellum. Symptoms are caused by a heat labile exotoxin elaborated *in vivo*.

There are two recognised biotypes of *V. cholerae*, the classical and El Tor variants, both of which cause essentially identical clinical disease. Biotype differentiation is based on laboratory tests, the most important of which depends upon the fact that El Tor variants are resistant to polymixin B on Mueller-Hinton agar (Han, Khie, 1963, and Gangarosa et al 1967) and to phage type IV of Mukerjee (1963) and agglutinate chicken red blood cells (Finkelstein and Mukerjee, 1963). The two biotypes are separated antigenically into two main serotypes, Ogawa and Inaba, and rarely a third type, Hikojima.

Symptoms

The incubation period is short, varying from several hours to a few days. There may be premonitory symptoms such as anorexia, irritability, abdominal discomfort and simple diarrhea. In many cases the onset is sudden, with profuse, watery diarrhea. Initially, the stool is brown with fecal matter, but soon the evacuations assume a pale gray colour with little solid material, have an inoffensive, slightly fishy odour and become projectile. Mucus in the stool imparts the characteristic "rice water" appearance. Tenesmus is absent, instead there may often be a decrease in irritability as enormous amounts of fluid are passed

effortlessly. Vomiting is common, occurring usually after the onset of diarrhea. Massive diarrhea may result in the lose of 10-15 per cent of body weight, causing profound dehydration and circulatory collapse. Peripheral pulses and blood pressure may be imperceptible, and heart sounds are rapid and faint while respirations are laboured and shallow. The skin is cold and clammy and doughy in consistency, and turgor is poor, the eyes are sunken and the tongue and mucous membranes are dry and hands and feet become wrinkled, as when long immersed in water, assuming the characteristic "washerwoman's hand" sign. Phonation may be impaired. The child is usually restless, extremely thirsty, and mentally lucid, although he may become obtunded. During the acute phase cyanosis may be present and painful muscle cramps may occur mimicking tetany. Bowel sounds are often hyperactive and a low grade fever may be present. Oliguria may be present until dehydration and electrolyte deficiencies are corrected ; patients who are inadequately treated or untreated for prolonged periods may develop uremia and acute renal failure. In totally untreated cases death may ensue within 24 hours.

Asymptomatic and Mild Cholera

In both epidemic and endemic cholera, children are more likely to have only inapparent infection or mild diarre hea, while adults are more apt to have severe disease and are more likely to be hospitalised. Children under the age of one year infrequently develop clinical cholera although inapparent infections are common. Only occasionally does infection result in cholera gravis. Numerous asymptomatic infections may be detected, particularly in household contacts, as demonstrated in bacteriological (Tamayo et al 1965) and serological (Benenson et al 1968) surveys. Milder forms of cholera, especially in household contacts, may be seen with simple diarrhea without rice water stools or significant dehydration. These cases cannot be differentiated by signs, symptoms or clinical course from other simple diarrhea.

Susceptibility

Cholera usually affects individuals of the lower socio-economic stratum because sanitary discipline is poorest in this group. There are no recognised nutritional or gastrointestinal factors which predispose to infection or illness, although those patients with underlying disease usually have a complicated clinical course. However, unknown factors related to age do influence host susceptibility to clinical disease after infection is acquired.

Differential Diagnosis

Diseases which may simulate cholera include : (1) food poisoning due to salmonella or staphylococcal enterotoxin. Unlike cholera, salmonellosis is usually a febrile disease. In staphylococcal food poisoning, vomiting precedes diarrhea, while the reverse is true in cholera. (2) Acute bacillary or amebic dysentery.

Although these diseases rarely cause massive diarrhea, they have been confused with cholera. Tenesmus, fever, blood and pus in the stools are common in these diseases and absent or rare in cholera. (3) Non-cholera vibrios occasionally cause an illness indistinguishable from cholera gravis (Carpenter et al 1965). (4) Epidemic or sporadic gastroenteritis of unknown etiology may mimic cholera except that purging in these illnesses usually lasts only 24 to 48 hours. Infantile diarrhea due to enteropathogenic *Escherichia coli* and rarely to viral agents may result in profound dehydration, shock, and death. (5) Other diseases have on occasion been confused with cholera. These include organophosphorus and metallic food poisoning such as zinc, cadmium, or arsenic; heat exhaustion; and falciparum malaria, intestinal melioidosis; pancreatic neoplasms; and mechanical obstructions of the bowel.

Cholera may sometimes presents a a mixed infection, *i.e.*, cholera vibrios with shigella or salmonella species or with various parasites.

Pathophysiology

The small bowel lumen in the site of the infection with *V. cholerae*. The organism adheres to the epithelial surface without penetrating the mucosa. Often imbedded in mucous the organism elaborates an exotoxin which in some manner functionally deranges intestinal epithelial physiology. Cellular response to infection is remarkably minimal, involving at most a non-specific increase in mucous producing goblet cells. Contrary to former beliefs, the small bowel mucosa is not denuded. Biopsy specimens at different levels of the bowel in severe cases reveal an intact epithelium (Gangarosa, et al 1960). Electron microscopic studies have demonstrated no specific changes (Elliott and Yardley 1967).

Organ and tissue changes which occur in cholera can be explained by severe water and electrolyte losses. The loss of electrolytes and fluid from the circulation and extracellular space accounts for the severe dehydration causing an increase in plasma protein concentration, hematocrit, and specific gravity of whole blood and plasma. The loss of bicarbonate, potassium, sodium and chloride is, essentially isotonic with plasma. This is reflected in usually normal sodium, chloride and potassium concentrations in blood. Stool bicarbonate loss results in severe acidosis manifested clinically by hyperventilation (Kussmaul respiration), vomiting, depression of the central nervous system, and chemically by depression of blood pH and plasma carbon dioxide content. Pediatric stool contains more potassium and less sodium than adult stool (Griffith et al 1967) (*Table I*). The concentration of potassium in the pediatric cholera stool is nearly twice that of the adult, resulting in a tremendous loss of cellular potassium manifested in the clinical findings of an abormal electrocardiogram with tall tented T waves (Carpenter et al 1967), ileus, and muscle cramps.

TABLE I

Electrolytes in the cholera stool

	Pediatric mEq/L	Adult mEq/L
HCO_3	35	45
Na	100	135
K	25	15
Cl	75	105
Tonicity	Isotonic	Isotonic

The major hemodynamic abnormality is a reduction in circulating blood volume, reflected in abnormally peaked P waves in the EKG (Carpenter et al 1967) which may produce a febrile response in some children. Acidosis causes a redistribution of blood from the peripheral to the central circulation (Harvey et al 1966). Focal myocardial necrosis, hypokalemic nephropathy or ischemic renal tubular necrosis due to prolonged circulatory collapse may be seen in cases in which treatment is long delayed or inadequate (Benyajati et al 1960), but this should be considered a complication and not a primary manifestation of cholera. The understanding of these pathophysiological changes, elucidated in large measure by the studies of Watten et al (1959) has led to a rational basis of treatment with a reduction in the mortality from 50 per cent to less than one per cent.

Treatment

1. *Principles* : The replacement of water and electrolyte losses in stool and vomitus is the basis of cholera therapy. Cholera is a medical emergency. Therapy should begin at once without waiting for laboratory results. Treatment consists of prompt and vigorous intravenous fiuid and electrolyte replacement to restore the circulation and correct dehydration, acidosis and potassium depletion. It has been repeatedly stated that cholera mortality is greater in children than in adults. This has been the case primarily because severe dehydration and its consequences can occur more rapidly in smaller children, and water and electrolyte replacement of the infant and child in inexperienced hands is associated with a high morbidity and mortality. In infancy water exchange in proportion to body weight is far greater in the adult. Fluid balances are more readily disturbed.

Provision should be made for the separate orderly collection and measurement of diarrheal stool, vomitus, and urine; "cholera cots" have been used extensively with excellent results (Phillips, 1964). The cot can be of canvas or burlap on a wooden frame with a four-six-inch hole where the patient places his buttocks. A plastic or rubber sheet with a sleeve through a hole facilitates the collection or liquid stool directly into a calibrated bucket which measures stool output. Urine should be collected and measured separately.

2. *Rehydration* : Fluid requirements forr ehydration are assessed on the basis of body weight and a clinical estimate of the

TABLE 2

Intravenous fluids useful for treatment of pediatric cholera

	Na	K	Cl	HCO_3	Lactate
	(millimols per liter)				
5:4:1 CRL Solution[1,2]	133	13	98	48	—
Lactated Ringers[1,3]	130	4	109	—	28
2 Parts Normal Saline to 1 Part 1.2% Sodium Bicarbonate[1,3]	154	—	110	55	—
2 Parts Normal Saline to 1 Part of 1/6 Molar Sodium Lactate[1,3]	158	—	105	—	53

1. Water must be administered orally to enable excretion of excess sodium.
2. Acetate may be substituted for sodium bicarbonate in the preparation of 5:4:1 or solution 3 in equal millimol amounts.
3. Potassium chloride (25 mEq/L) should be added, preferably after urine flow is observed.

severity of dehydration. This is based on the quality of the peripheral pulses, the degree of skin turgor and measurement of blood pressure. Intravenous rehydration is the route of choice. Infusion of fluids subcutaneously is to be avoided since absorption by this route is slow and cannot adequately meet the large volume needs. Severely dehydrated patients, as judged by clinical estimates should immediately receive a volume equivalent to approximately 10 per cent of body weight. A base-line weight is helpful but can be delayed until fluids have been started.

It is important to establish an intravenous route through which fluid can be given rapidly. Even in severe shock, an antecubital vein can usually be used in most older children and adults. In infants, a 21 gauge thin-walled scalp vein needle should be used. If a suitable peripheral vein in the antecubital fossa, scalp or dorsum of the foot cannot be readily found, other sites of infusion should be sought, *i.e.*, femoral or external jugular vein the anterior fontanelle, or the bone marrow of the tibia. When the femoral vein is used a second infusion should be started as soon as a peripheral vein is available. Intravenous solutions can be infused at a rate of 1 ml/kg/minute. This rate of infusion should be continued until the reappearance of normal vital signs, skin turgor, and moisture to the

mucous membranes. During the time the patient is receiving initial rehydration a rapid physical examination should be performed.

Plasma protein or specific gravity, hemoglobin, or hematocrit should not be used as a method of determining the degree of dehydration since, in children, values do not accurately reflect the state of hydration. In addition children with cholera are often anemic and hypoproteinemic.

A variety of electrolyte solutions are available or may be prepared for treatment of pediatric patients (*Table 2*). At the Pakistan-SEATO Cholera Research Laboratory in Dacca (East Pakistan) an electrolyte solution has been used in adults and children for many years with excellent results. It contains (per liter of solution) 133 mEq of potassium, 48 mEq of bicarbonate and 98 mEq of chloride, prepared by adding 5 grams of sodium chloride, 4 grams of sodium bicarbonate and 1 gram of potassium chloride to a liter of water. This solution approximates the concentration of salts in the adult cholera stool and is also used for children if oral water is given to permit excretion of excess sodium in the solution. Additional potassium given by mouth as potassium salts, or potassium-rich foods may be required for some children. Replacement should be based on average stool potassium concentrations of 25 mEg/liter. If special solutions are not available, satisfactory commercial preparations can be obtained : two parts of isotonic sodium chloride mixed with one part of isotonic (1.2%) sodium bicarbonate or with isotonic (one-sixth molar) sodium lactate can be infused. Acetate may be substituted for bicarbonate. It has less tendency to over correct acidosis and can be autoclaved.

Severely acidotic children benefit from rapid correction of acidosis as part of their initial rehydration. Sodium chloride solutions should not be used alone, since the correction of the blood volume when acidosis remains uncorrected may lead to pulmonary oedema (Harvey 1968). Initial therapy usually restores a child to an alert mental state. If the child does not respond a search for complications, such as hypoglycemia or hypokalemia, should be made, since both are frequently associated with pediatric cholera. The routine addition of one per cent glucose to intravenous solutions will prevent hypoglycemia (Hirschhorn et al 1966). Symptomatic hypoglycemia may be corrected with 25-50 ml of a 50 per cent glucose solution intravenously.

3. *Maintenance* : Solutions used for rehydration may also be used for maintenance if supplemental water is given by mouth as needed. The rate of administration of maintenance therapy depends on the careful collection and measurement of liquid stool along with estimation of insensible, and urinary losses ; replacement is on a volume-for-volume basis. Vital signs and stool volume should be checked hourly in children who

are purging heavily. Intake and output should be measured and recorded in less severe patients at 4 to 8 hour intervals. Intravenous therapy should continue until diarrhea ceases. Whenever possible, children should be treated in an area separate from adults, equipped with appropriate supplies and staffed by persons trained in pediatric nursing and treatment. Mothers may be helpful in administering water and other fluids by mouth.

4. *Oral Therapy* : An oral solution containing electrolytes and glucose which has been shown to be effective for the maintenance of hydration in adult cholera patients (Nalin et al 1968) has also been shown to be effective in children (Nalin et al in preparation). The solution contains 120 mEq/L of sodium, 25 mEq/L of potassium, 48 mEq/L of bicarbonate and 97 mEq/L of chloride and is made up by adding 63 grams of sodium chloride, 28 grams of potassium chloride, 60.5 grams of sodium bicarbonate and 300 grams of glucose to 15 liters of water.

The oral solution does not eliminate the need for initial intravenous therapy to treat shock in severe, acute cholera, nor the need for careful intake and output records under the supervision of specially trained staff. However, the oral solution can eliminate the need for over three quarters of the intravenous maintenance requirements. The ingredients of the oral solution are cheap and widely available in virtually all areas affected by cholera. The ingredients can be preweighed and stockpiled for use in cholera epidemics.

5. *Antimicrobial Therapy* : Chemotherapy has been shown to be a valuable adjunct in shortening the duration of diarrhea and the duration of excretion of *V. cholerae* (Carpenter et al 1966). Tetracycline is generally considered the drug of choice (Wallace et al 1968). It should be given orally in a dose of 20-40 mg/kg every six hours for five days. Antibiotic therapy should be started after vomiting subsides, that is, after initial rehydration and correction of acidosis; parenteral antibiotic therapy is unnecessary. The side effects of tetracycline make furazolidone the drug of choice in infants and small children. Chloramphenical is also effective but because of its dangerous, although rare, hematopoietic side effects its use should be restricted. Sulfa drugs and streptomycin, commonly found in diarrhea mixtures, are less effective and associated with bacterial relapse.

6. *Other Measures* : Blood, plasma, and plasma expanders should not be given. Vasopressers and cardiorespiratory stimulants are contraindicated. Atropine and steroids are unnecessary and may be harmful. Kaolin and kaopectate are of no clinical value. Bacteriophage treatment is of no value.

Prophylaxis

Chemoprophylaxis should be considered to prevent delayed cases in high-risk groups, such as family contacts,

exposed to the same contaminated food and/or water supply. McCormack et al (1968) showed that tetracycline given in a single daily does of I gram for five days eliminated infection and prevented cholera in household contacts. Bacteriophage used in prophylaxis of family contacts has no value.

Complications

The rapid infusion of bicarbonate to correct acidosis or of glucose to correct hypoglycemia may depress the blood potassium levels and increase the need for potassium therapy. Ileus may occur and requires additional pottassium. Tetany is infrequently encountered as the result of over correction of acidosis and can be controlled with intravenous calcium gluconate.

Prognosis

The case fatality rate of untreated patients in some epidemics has reached as high as 70 per cent. With adequate fluid and electrolyte replacement the mortality does not exceed one per cent, and most patients have an uncomplicated course with complete recovery.

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