



# Technical

# Discussions



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STUDIES AND STRATEGIES TO REDUCE MORBIDITY AND MORTALITY FROM ENTERIC INFECTIONS

CLINICAL DIAGNOSIS AND TREATMENT, INCLUDING ORAL  
AND INTRAVENOUS REHYDRATION

1. Salmonella: S. typhimurium and S. typhi
2. Shigella: S. dysenteriae 1
3. Vibrio cholerae
4. Enteric infections from other causes, including the symptom known as "travelers' diarrhea"

by

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CLINICAL DIAGNOSIS AND TREATMENT, INCLUDING ORAL  
AND INTRAVENOUS REHYDRATION

## INTRODUCTION

The syndrome of an infectious disease is conditioned by the morphological and physiological disturbances caused by the agent of infection, and the wide range of intensity of these disturbances is a consequence of the variability of the determining factors involved, i.e., the pathogenicity of the infecting species or strain and the degree of susceptibility and resistance of the host. The microorganism may undergo mutation or alteration of its genotype and an increase in its virulence (lysogenic conversion of Corynebacterium diphtheriae, multiple "episome" resistance factor of Salmonella typhi and other bacterial species). The host is susceptible when the agent of infection satisfies its vital needs for development and multiplication in his tissues, but if he is able to change his physiological condition in response to the presence of the microorganism and react effectively, his condition will be resistant. Thus a highly susceptible individual may become a strongly resistant one.

Failure to adapt to the environmental disturbances of the external or internal surroundings is frequently genetic in origin. Immunogenic deficiencies impair the resistance in the event of infection. Other factors undermining the immunity mechanisms and increasing the severity of the disorder are malnutrition, physical and emotional tension, metabolic and neoplastic diseases, etc.

The bacteria determining enteric infections may be distinguished by their invasiveness and/or their toxigenicity. The salmonellae and shigellae exemplify invasiveness; the Cholera vibrio and Escherichia coli exemplify toxigenicity.

## SALMONELLOSIS

Microorganisms of the genus Salmonella are able to penetrate through the intestinal epithelium and invade the lamina propria, where they proliferate. Salmonellae which specifically infect man, e.g., S. typhi, penetrate beyond this structure and spread to the tissues via the lymph and blood circulation and infect the cells of the reticulo-endothelial system, especially of the spleen, the liver, the lymph nodes and the bone marrow. Their commonest clinical expression is septicemia. In the lamina propria they cause a mononuclear cell reaction. Salmonellae which infect men and the lower animals indifferently produce in the lamina propria an inflammatory reaction of polymorphonuclear neutrophils which eliminate the bacteria fairly rapidly.

Infection by these salmonellae frequently causes enteritis. When their pathogenicity is particularly great, they invade the internal tissues via the circulation and give rise to focalized pyogenic infections. The prototype of these microorganisms is S. enteritidis, serotype typhimurium.

Enteritis caused by salmonella has a short period of incubation which probably reflects the strength of the infecting dose. It causes inflammation of the mucosa of the small intestine and the colon, hypertrophy of the lymph follicles and occasionally ulceration.

### Clinical Symptoms

#### Period of Incubation

Average 8 to 24 hours, with a minimum of 6 hours and a maximum of 48 hours

#### Nausea and Vomiting of Average Intensity

#### Diarrhea

Watery, varying in degree of severity; may contain mucus and be tinged with blood. Lasts 3 to 5 days and clears up of its own accord. In exceptional cases may last 2 weeks

#### Fever

Approximately 38 to 39° C.

#### Abdominal Colic

Excretion of salmonella via the feces is of short duration. However, in some patients it continues for long periods, and in exceptional cases they become chronic carriers.

Occasionally, certain salmonellae produce septicemia and metastatic focal infections, bronchitis, pyelonephritis, meningitis, osteomyelitis, etc.

#### Treatment

The main aim of the treatment is to correct the hydroelectrolytic imbalance caused by the diarrhea. There is no clear proof that antimicrobial agents shorten the duration of the disease or the period of elimination of salmonellae via the feces. In some cases it has been proved that they lengthen the period. The use of medicaments which reduce the motility of the intestine is proscribed, since they are liable to aggravate the disease by inhibiting the effective elimination of the pathogenic bacteria through the bowel motions. Focalized infections are treated by surgical drainage. At times the use of antimicrobial agents such as chloromycetin or ampicillin may prove effective.

## TYPHOID FEVER

Malnutrition and inadequate treatment, especially with antimicrobials, alter the typhoid fever syndrome.

Clinical SymptomsPeriod of Incubation

7 to 14 days, with an extreme range of 3 to 60 days.

Onset

Warning symptoms lasting 3 to 5 days:

Asthenia

Anorexia

Adynamia

General indisposition

Course of Illness

<u>Syndrome</u>	<u>Percentage</u>
Fever	100.0
Headache	82.0
Diarrhea	63.0
Abdominal pains	56.0
Vomiting	48.0
Myalgia	45.0
Arthralgia	45.0
Meteorism	42.0
Pharyngitis	42.0
Hepatomegalia	29.0
Roseola	24.0
Epistaxis	20.0
Icterus	15.0
Effects on the central nervous system (confusion and delirium)	12.0
Splenomegaly	11.0

The fever rises in stages, reaching its peak in a few days and remaining stationary at its highest level for 10 to 15 days, temperature 39 or 40° C, and even higher. In women and children the pulse keeps pace with the temperature, whereas in men relative bradycardia is frequently found. Dicrotic pulse is common.

At the end of the first week of the illness, small roseola maculopapular lesions appear, 2 to 5 mm in diameter. They are few in number, seldom exceeding 20, and they disappear under pressure. They are found in the flanks and at the base of the thorax, and repeated outbreaks may occur. Delirium is as a rule peaceful, but the patient may become violent and aggressive. Sleep is fitful. Defervescence begins in the third week; the temperature drops gradually and becomes normal by the fourth week, and the remaining signs and symptoms disappear. The average duration of medium grave cases is four weeks.

The complications we have observed most frequently are the following:

	<u>Percentage</u>
Hydroelectrolytic imbalance	43.8
Bleeding of the digestive tube	20.8
Changes in coagulation tests	15.9
Hepatitis	7.7
Bronchopneumonia	1.7
Miocardia	1.4
Intestinal perforation	0.9

#### Treatment

If the strain of S. typhi is sensitive to chloramphenicol, it should be administered in the following form: 500 mg. per os every 4 hours until the temperature returns to normal, continuing with 500 mg. every 6 hours for 2 to 3 days, up to a maximum of 8 to 10 days, the treatment being completed in 15, 18 or 21 days with 500 mg. every 8 hours. The total number of days will depend on the time taken for the disease to evolve after the treatment begins. Intravenous or intramuscular administration is used when the patient cannot tolerate the medicament taken by mouth. The dose of chloramphenicol for children is 25 to 75 mg. per kg. body weight per day, whatever the method of administration.

When the strain is resistant to chloramphenicol, ampicillin is used in doses of 1 gr. every 4 hours, intravenously in the first place. Once the temperature is normal, the same dose is administered every 6 hours for another 8 or 10 days, by the intravenous or intramuscular route. It is continued with 500 mg. per dose every 6 hours up to 15 to 18 days in all. In children the dose is 100 to 200 mg. per kg. body weight per day, the treatment beginning intravenously. The dose is divided into four portions administered every 6 hours for 5 days, and it is continued by the intramuscular or oral route for up to 7 days more. Treatment with trimethoprim and sulfamethoxazole in doses of 8 mg. and 40 mg. respectively per kg. body weight per 24 hours over a period of 10 days can also be useful.

It is of the utmost importance to maintain the hydroelectrolytic balance. If this is neglected the disease becomes aggravated, and symptoms of irreversible disseminated intravascular coagulation may appear.

The patient must have complete rest and a balanced diet poor in residues to avoid meteorism. Vitamin C and B complex should be administered for at least a week after the antimicrobial has been suspended.

## SHIGELLOSIS

Shigellae invade the epithelial cells of the intestinal mucosa, where they multiply. S. dysenteriae 1 tends to spread in epidemic form, producing serious clinical symptoms and developing an exotoxin with a cytolytic and neurotoxic action. Nevertheless, it has been demonstrated experimentally that its pathogenicity is directly linked with its invasive power; the exotoxin helps to increase its virulence, principally by its cytolytic action on the cells of the intestinal epithelium. Shigellae colonize the large intestine, causing evacuation of the caliciform cells, serious losses of epithelial cells with ulceration, fusion of the villi and formation of cryptic abscesses, and inflammatory acute cellular and vascular reaction. Large segments of the colon and the sigmoids may be found to be covered with a fibrinous exudate containing many polymorphonuclear neutrophils which, when shed, leave irregular surface ulcerations.

The period of incubation varies from 36 to 72 hours. The initial symptoms are fever and painful intestinal cramps, followed by diarrhea, which may later turn into dysentery, with straining, evacuations containing mucus, blood and pus, and serious general symptoms.

The spectrum of severity of the disease is very wide, depending on the species and strain of the infecting agent, and the resistance mechanisms of the subject infected. The mild form, without fever and with slight diarrhea, is the most common. Serious shigellosis may cause loss of liquids and electrolytes, making the prognosis gloomy, especially in children and old people. In such cases, sigmoidoscopy reveals intense hyperemia, multiple small areas of bleeding, and secretion of purulent mucus. Acute symptoms may last for a week to 10 days. Evacuation becomes less frequent, the pain and the straining diminish, and temperature becomes normal. The convalescent period is several weeks.

### Treatment

Patients only slightly infected can be cured without the need for antimicrobials. In serious cases, tetracycline, chloramphenicol or ampicillin are used, the last-named particularly in cases where the shigella shows multiple resistance. It is therefore recommended that tests be carried out on the susceptibility to antimicrobial agents using the strains obtained in stool cultures.

It is essential to reestablish the hydroelectrolytic and basic acid balance. When there is vomiting, the intravenous route should be used.

A mixture of glucose solution 5 per cent with physiologic salt solution in equal parts is recommended, in doses of 30 ml. per kg. body weight per day. As the diuresis and circulation improve, the tempo of administration is reduced. Use may also be made of the 3:2:1 mixture (3 parts serum with 5 per cent glucose, 2 parts physiologic salt solution and one part sodium lactate 1/6M). In very serious cases, blood transfusions or plasma injections may be used. The diet should be poor in residues and protein-rich.

#### CHOLERA

Pathogenic mechanisms of the Vibrio cholerae: It has been amply demonstrated that this microorganism develops an enterotoxin which causes the disease and that the physiopathological and metabolic disturbances due to cholera are the direct consequence of the loss of liquids and electrolytes in the small intestine resulting from the enterotoxin. The colon maintains its normal functions during cholera. Experimental studies have proved that the enterotoxin adheres rapidly and irreversibly to the intestinal epithelium. After an interval of approximately 30 minutes, the breakdown in the transport of liquids and electrolytes becomes evident. This reaches its peak in 3 to 5 hours and gradually decreases by 12 hours, probably because of the death of the cells affected and their replacement by others. This phenomenon takes place along the whole length of the small intestine. Very careful histological studies have demonstrated that there is no morphological damage to the cells concerned.

The enterotoxin increases the activity of the adenylyl cyclase and at the same time there is an intracellular increase in cyclic adenosine monophosphate (cAMP) which increases the intraluminal chlorine secretion, bicarbonate and water. The isotonic liquid secretion lasts as long as the functional life of the epithelial cell persists.

The clinical symptoms of the disease have a wide spectrum of severity, which has given rise to names like "choleraic diarrhea," "cholerae," "cholera gravis." The ratio of asymptomatic infection to clinical cases is 4 to 1 for El Tor and 1 to 7 for the classic biotype; the ratio between moderate and serious cholera in El Tor infections is 7 to 1, and for the classic cholera vibrio 1 to 1.

In their mild form, the clinical symptoms last approximately 5 days, but 48 hours is common. Patients have several evacuations a day, the volume in the case of adults being less than one liter in 24 hours. If water and food are ingested in sufficient quantities, the patient will not suffer from hydroelectrolytic imbalance, although at times he may complain of cramps, nausea, and vomiting. This form somewhat resembles enteritis of other etiologies, such as shigellosis and enteropathogenic Escherichia coli diarrheas. These cases do not require specific treatment; nevertheless, they are very important from the epidemiological standpoint, since they spread the vibriion widely because of the mobility of the patients.

The clinical symptoms of the severe form of the disease are related to the loss of large quantities of water and electrolytes. The loss of water and isotonic salts is at the expense of the extracellular compartment, and is manifested in the form of hemoconcentration and diminution of the volume of blood in circulation. Patients with serious cases not undergoing treatment may have a deficit of isotonic liquids, from 10 to 12 per cent of the total body weight. Higher losses are frequently fatal. The final result is hypovolemic shock.

The loss of large quantities of bicarbonate in the feces, with inadequate production of the substance by the kidneys and acid excretion during oliguria or anuria, produces acidosis due to base deficit. In the more serious forms the bicarbonate values frequently drop to under 10 mEq./L and be as low as 5 mEq./L. This means a total bicarbonate loss of approximately 160 mEq. in a person weighing 40 kg. In the circumstances, the arterial pH values may drop to 7.00. Acidosis may produce pulmonary hypertension and cause pulmonary edema in patients rehydrated without concurrent correction of the acidosis. Potassium is lost via the diarrheal feces and through the damage caused to the renal potassium conservation mechanism by acidosis.

The period of incubation of cholera is 24 hours to five days. It has been pointed out that the cholera vibrio may be isolated from fecal matter formed 24 hours, and up to 3-5 days, before the diarrhea begins. The disease may have a slow onset, with slight diarrhea lasting 24 to 36 hours, or may begin abruptly with profuse diarrhea. The clear liquid vomit secreted by the upper portions of the small intestine may be very abundant. As a rule, nausea is slight. Evacuations rapidly take on the "rice water" look, and adults may eliminate up to one liter per hour. If the patient is correctly handled, with water and electrolytes, the diarrhea may terminate in one to six days. The great loss of isotonic liquid through the vomit and evacuations produces a deficit within four hours, although commonly it may take 24-48 hours after onset. The patient complains of intense thirst, which appears when the loss of liquid is equal to 2 or 3 per cent of the body weight. If the loss is higher, we get postural hypotension, accompanied in severe cases by fainting and syncope when the patient stands, oliguria which may amount to anuria, and cramps in the muscles of the extremities. The voice is weak and aphonic. Extreme weakness and lethargy occur when the losses reach 5 to 8 per cent of the body weight, and stupor and coma when they are greater than this. Physical examination may show tachycardia and loss of turgescence of the skin. Systolic pressure falls and the pulse is rapid. The temperature is commonly normal in adults, but in 80 per cent of cases in children the rectal temperature is high. The rate of breathing increases and, if the acidosis is not treated, respiration may take on the Kussmaul characteristics. Cyanosis appears at the roots of the fingernails, the patient is cold and the skin is moist. The eyes are sunken and, in children, the fontanelles as well. The mucous membranes are dry.



Treatment

The loss of isotonic solution in large quantities via the intestine necessitates urgent treatment to replace liquids and electrolytes. The following table, taken from Carpenter, shows the composition of the diarrheal liquid:

<u>Ions</u>	<u>mEq./liter</u>
Sodium	126 <u>9</u>
Potassium	19 <u>9</u>
Bicarbonate	47 <u>10</u>
Chlorine	90 <u>9</u>

Some patients eliminate 500 and even 1,000 ml an hour. This means considerable loss, and the hydroelectrolytic and basic acid imbalance leads rapidly to hypovolemic shock and death. In severe cases a start should be made with the administration of solutions by the intravenous route, later by mouth, the oral route being preferred in cases of average seriousness with no vomiting. The amount of water to be replaced is calculated on the basis of the hematocrit and the clinical symptoms of the patient.

The solutions used intravenously are the so-called 5:4:1 and 2:1.

<u>Type of Solution</u>	<u>mEq./sodium/L</u>	<u>mEq.K/L</u>	<u>mEq.Cl/L</u>	<u>MEq.Bicarb./L</u>	<u>Osmolarity</u>
5:4:1*	133	14	99	48	294
2:1**	156	0	104	52 (with bicarbonate or lactate)	312

\*5 gr. sodium chloride, 4 gr. sodium bicarbonate, 1 gr. potassium chloride in 1 liter of water

\*\*Salt: basic

The development of oral therapy for cholera has brought the solution of very serious problems, in particular that of availability of intravenous solutions, which in epidemic situations are limited and reserved exclusively for very serious cases. Glucose administered by mouth increases the absorption of electrolytes via the small intestine, and restores the hydroelectrolytic and basic acid balance, a phenomenon not affected by clinical cholera. The solution recommended is as follows:

<u>Solution</u>	<u>mEq./Liter</u>
Glucose	120 mMol/Liter
Sodium	100
Potassium	10
Chlorine	70
Bicarbonate	40

Whatever the solution selected, it should contain potassium and bicarbonate. With regard to antimicrobials, tetracycline reduces the volume and duration of the diarrhea and curtails the period of excretion of the cholera vibron.

New agents of infection have been cited as causes of enteritis, perhaps the most important being enteropathogenic Escherichia coli. Some serotypes cause gastroenteritis in human beings, and their pathogeny is very similar to that of cholera vibrio. They colonize the stomach and the upper parts of the small intestine, duodenum and jejunum. But the infection can spread more widely. The microorganisms are eliminated from these areas 7 to 10 days after the acute stage, but they may persist for several weeks. There is no penetration by the enteropathogenic strains to the intestinal epithelium, or morphological alteration of this structure. The diarrhea is caused by secretion of isotonic liquid by the intestine, and no doubt also by mediation of the adenyl cyclase and the intoxication of the mucosa by cholera toxin. The illness caused by E. coli is of short duration, and the diarrheal liquid is moderate in amount. The mucosa of the small intestine is extremely sensitive to the enterotoxin of E. coli, whereas the colon is resistant. Rowe et al suggest that a serotype now known as O148:K:H21 caused a syndrome known as "travelers' diarrhea." Gorbach has encountered other strains, also productive of enterotoxin, which cause diarrhea. It seems probable that certain as yet unidentified serotypes and strains of E. coli have the peculiarity of producing this enterotoxin, and at the present time it is thought that E. coli acquires this peculiarity by means of an episome transferred by conjugation.

Kean et al have made a careful study of the "diarrhea of travelers to Mexico syndrome." The symptoms associated with this disease are abdominal pains, nausea, vomiting, fever, and headache. In most cases, the syndrome is mild, but in a small percentage of cases it may be serious. Treatment of serious cases of infection by enteropathogenic E. coli is aimed mainly at restoring liquids and the electrolytic and basic acid imbalance in the same way as is recommended for cholera. The use of antimicrobials does not bring about an improvement, so that they should be prescribed only in serious cases. Other nontoxicogenic strains of E. coli invade the epithelium of the colonic mucosa in the same way as shigellae.

Finally, Clostridium perfringens and Staphylococcus aureus may produce enteritis by mediation of enterotoxin.

#### SUMMARY AND COMMENTS

1. Infectious agents causing enterocolitis exert their pathogenic action through two mechanisms: invasiveness and/or toxigenicity. Salmonellae, shigellae and certain strains of Escherichia coli are invasive, while vibrio cholera and enteropathogenic E. coli produce exclusively toxigenic action. The clinical difference between these two types is fever, which is characteristic of the invasive microorganisms.
2. The clinical severity depends on various factors including malnutrition, which causes deterioration of the resistance mechanisms of the host.
3. The most common disturbance caused by the serious forms of these ailments is hydroelectrolytic and basic acid imbalance, which may lead to hypovolemic shock and irreversible disseminated intravascular coagulation.
4. The treatment of these disorders involves restoration of liquids, electrolytes and pH at all costs, this being done by administering appropriate salt solutions. In serious cases these are given intravenously; in moderate cases or when the severity has abated, the oral route may be used for the administration of solutions containing glucose, a substance which favors the absorption of electrolytes.
5. The use of antimicrobials is restricted only in the case of typhoid fever and the treatment of serious cases of other enteric infections. Imprudent use of these agents should be proscribed, because it has been proved that they prolong the period of elimination of the agent of infection via the fecal matter and because they upset the ecology of the intestinal tract, thus favoring the appearance of multiple resistance in enteric pathogens and promoting the phenomenon of interbacterial conjugation.
6. Medicaments which reduce the motility of the intestine should be proscribed, since they inhibit this cleansing mechanism.
7. Epidemiologic surveillance of the strains producing enterocolitis is recommended with a view to detecting changes in susceptibility to antimicrobials and adjusting the treatment accordingly.
8. It would be useful to publish a medical bulletin giving clinical, therapeutic and epidemiological information to doctors and nurses practicing in rural areas where the problem of enteric infections is acute.
9. In rural areas where there is no doctor, paramedical and auxiliary personnel should be trained in the correct way of administering solutions and, above all, in ways and means of preventing these infections so as to avoid epidemic outbreaks with grave danger to the community.

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