CHOLERA

By PROFESSOR BRIAN MAEGRAITH, M.A., M.B., M.R.C.P., D.PHIL.

School of Tropical Medicine, Liverpool

Definition

Cholera is an acute, self-limiting, often fatal infectious disease of short duration caused by a specific organism, *Vibrio cholerae*, which multiplies in the gut contents but does not invade the blood stream or tissues. It is characterized by copious watery diarrhoea, vomiting, muscle cramps, severe dehydration, vascular collapse and various complications, especially suppression of urine and acute uraemia.

Distribution

Cholera has a strictly endemic distribution in certain tropical regions of high humidity and temperature, namely Bengal and Madras in India and the Yangtse valley in China. The most important endemic focus is that in Bengal, which is confined mainly to localities along the River Hooghly. Other suspected but not confirmed endemic foci are situated in Burma and the Philippines.

Local epidemic or pandemic extensions of the disease have occurred from time to time along trade routes and other lines of communication.

Aetiology

The causative organism *Vibrio cholerae* belongs to a group of bacteria which are morphologically similar to, but antigenically and biochemically distinct from, other vibrios. The cholera vibrio is small, comma-shaped and motile. It is gram negative and grows easily at 37°C. in ordinary bacteriological media. Vibrios are divided into groups depending upon their antigenic pattern. Those known to cause cholera have a common H antigen and specific O antigens. There are three principal strains, i.e. the Inaba, Ogawa and Hikojima strains. One of these usually predominates in outbreaks, but sometimes the prevalent antigenic strain changes.

A fourth strain, called the El Tor vibrio, appears, under some circumstances, to be able to produce the disease. It is distinguished from the other cholera vibrios by its haemolytic action *in vitro*.

In nature the organism is pathogenic only to man. Other animals are not infected. A con-

dition somewhat resembling cholera can, however, be induced by artificial gut infection of young guinea-pigs and rabbits.

In the human case the vibrio grows and multiplies almost entirely in the lumen of the gut. It does not penetrate beyond the submucosa of the intestinal wall and is never found in the blood stream or in the urine. In the clinical attack it is present in enormous numbers in the faeces and vomitus.

In most cases the vibrio may be found in the faeces and vomitus for about five days only. Occasionally it may persist for as long as a few weeks. There are no true "carriers" of the disease in whom the infection persists for longer periods.

It appears, therefore, that the maintenance of endemicity in a given area must depend on the direct spread of infection from case to case, the mode of transmission being mainly through faeces. Individuals may become infected without showing any clinical evidence of the disease. It is thus not necessary to have overt cases for transmission to occur.

The organism can survive on moist clothing for up to three days. It dies rapidly in pure water but survives for days (maximum of six weeks) in slightly dirty water containing salts and organic matter. It is easily killed by moderate heat (55°C. for $\frac{1}{2}$ hr.) and acid.

In a community the infection spreads most commonly through infected water (including ice and cola drinks) contaminated with faeces. Other potable fluids including milk, cold cooked foods, vegetables sprinkled with water and uncooked fruits may also be concerned with the spread of the infection. Spread may occur from case to case through direct contact with faeces or vomitus. The only important living agent of transmission is the domestic fly.

In endemic areas most cases occur in the hot moist season, possibly because of the mechanical flushing of local filthy water supplies. Thus the incidence is highest in Bengal in the early rains (May, June and July) and lowest in the dry weather.

Epidemics arise from the introduction of the

vibrio by infected individuals, who may or may not show clinical signs of infection. Once the disease is introduced it spreads by the same means as in the endemic area. Where sanitary conditions are good there is little chance of spread. Where they are so bad that water supplies can be continually infected, cholera becomes rapidly established. Since the individual case is usually infective for only a few days the extension of the disease from endemic areas is largely limited by the rate of travel. Modern transport is a potential threat to insanitary areas outside the endemic foci, and rigid international control is necessary to keep the disease confined.

In non-endemic areas prevention of the import of the disease is a matter of sanitary control and quarantine of ships and aircraft from infected areas and the isolation of suspected cases. Where cholera has appeared local water supplies must be examined and protected from pollution. Chlorination will rapidly destroy the vibrio. Individual drinking and washing supplies should be boiled or chlorinated before use, and the strictest attention must be paid to the preparation and consumption of food. Anti-fly precautions should be enforced.

Individual or mass protection by the use of vaccines of dead vibrios, preferably local strains, should be carried out if possible. Individual injection is given in two doses (first dose 0.5 ml. and second dose 1 ml.) a week apart. When vaccination is used for mass protection, for example during an epidemic, a single dose of 1 ml. is employed.

Modern vaccines do not usually produce febrile reactions. They endow some immunity, which is effective for four to six months. Repeated vaccination is necessary in individuals residing for longer periods in infected areas.

Resistance to Infection

In a group of individuals exposed to the same source of infection by no means all may become infected. Of those infected some will show the fully developed syndrome, others may have no clinical ill-effects. It is believed that certain individuals may thus present some natural resistance to infection. The acidity of the gastric juice may act as a barrier to infection of the gut, the vibrios being highly susceptible to an acid environment; reduction in gastric acidity may predispose to infection.

Newcomers to the endemic area are believed to be more likely to become infected, but this is not certain. There is little evidence of herd immunity in the sense that it exists in malaria; the local population of an endemic area may be highly susceptible during outbreaks.

The cholera outbreak in a community is self-limited. It tends to die out after reaching its peak. This may be in some measure due to the large number of subclinical cases which develop, or to the acquisition of temporary individual immunity. It has been demonstrated, however, that one attack does not protect against subsequent infection, except partially for a very limited period.

In epidemics a smaller proportion of the local populations may be infected than might be anticipated. Napier, for instance, has pointed out the striking difference between the infection rate of cholera (about one in three) and smallpox, in an exposed community in which there is free intercommunication.

Antibodies, including agglutinins, and some measure of protection against infection are produced in animals by the inoculation of killed vibrio cultures intramuscularly or subcutaneously. Such inoculations may afford considerable protection in man for a few months at a time, certainly not more than six months. It is said that inoculation with the local strain is most efficacious.

Race, sex and age appear to play little part in the incidence of the disease. Malnutrition and poor health probably predispose to infection, but otherwise healthy subjects are often readily infected.

Pathology

Pathogenesis

In cholera the organisms remain in the gut and do not invade the blood stream. In the gut the vibrios multiply rapidly and cause the loss of enormous quantities of water and salt from the tissues, through the intestinal epithelium into the lumen and so outside the body. This is the basic physiological lesion. Certain local effects on the gut wall may be produced. There is often considerable shredding of the epithelium and in the later stages some bleeding into the lumen. There is never any deep ulceration of the intestinal wall.

The mode of action of the infection is not understood. No soluble toxin has been identified. It has been shown, however, that poisonous substances or endotoxins are formed *in vitro* during the growth and lysis of the vibrio, and it may be that these are involved. The endotoxin has been shown in animals to affect the permeability of the gut wall to electrolytes. Its effect can be neutralized to some extent by antibodies derived from injection of killed cultures of cholera vibrios. It is probable that the whole syndrome arises as a result of the action of a vibrio or its products such as this 'endotoxin' on the physiological permeability of the intestinal wall.

The loss of fluid and electrolytes is rapid and severe. A state of mixed salt and water dehydra-

tion is quickly achieved. Relatively greater losses of sodium than chloride occur owing to the preponderance of fluid loss from the gut. Some degree of acidosis and haemoconcentration results.

The serious dehydration itself affects the circulating plasma volume, which is often further reduced by the appearance of vascular collapse. Haemoconcentration is therefore pronounced in severe cases. The viscosity of the blood increases considerably and the efficiency of the circulation is correspondingly diminished. The appearance of vascular collapse accentuates the circulatory difficulties. The combination of dehydration and shock bring about functional and structural tissue damage, particularly in the kidney.

Morbid Anatomy

The information regarding the morbid anatomy of cholera is surprisingly incomplete. The tissue changes are basically non-specific and the lesions in the internal organs appear to be those which arise from the prevailing dehydration and/or vascular collapse.

Rigor mortis develops rapidly. The muscles are deep red and dehydrated; violent post-mortem contractions may occur. The tissues are dry. The blood is viscid. There may be scattered petechial haemorrhages in the mucous membrane of the intestines and in the pericardium.

Changes in the organs are commoner in cases which survived to the late stages before death. The anuric and uraemic case may present kidney lesions similar to those often met in other examples of the renal anoxia syndrome. There may be irregular ischaemia of the cortex involving the glomeruli in a patchy manner, some medullary congestion and epithelial degeneration and desquamation evident particularly in the cortical tubules which, together with the collecting tubules may contain casts of albuminous material and epithelial debris. On the other hand, there may be little evidence of structural change in the kidneys of the anuric case, especially if death has occurred soon after the renal failure. The liver may be congested and show some degenerative lesions, mainly centrilobular. The gall bladder and bile ducts are filled with dark viscid inspissated bile.

Pulmonary oedema may be present in shocked cases. Otherwise the lungs are shrunken and anaemic.

Clinical Pathology

Blood Cells

The dehydration and loss of plasma volume cause rapid haemoconcentration. In severe cases the blood is viscid and the erythrocyte count may

become as high as 8 or 9 million cells per c.mm. The white cell count is correspondingly increased.

The Blood

The viscosity and specific gravity is increased, roughly in proportion to the loss of plasma volume. The specific gravity of normal blood measured by the method described in the section on treatment is about 1054. In severe cases at the height of 'fluid loss' it may be 1060 or even more.

The chemical constituents of the blood depend primarily upon the state of dehydration and the successful function or otherwise of the kidneys. In the severe case the total chloride concentration is low; the sodium is lower in proportion; the potassium is usually unchanged.

The blood urea N concentration is raised above the normal range in most cases. In the anuric case it rises steadily to reach very high figures. In recovery after anuria it falls rapidly.

Urine

In the dehydrated case the output is low. There may be no urinary secretion. The specific gravity may be high and the urine deeply pigmented. Nevertheless, the urea and electrolyte content is low and there may be no chloride or sodium. Albumin and casts are present in the early acute attack. After recovery the electrolytes turn rapidly, but owing to the slow recovery of the renal epithelium it may be some time before the concentration of the urine is re-established.

Clinical Picture

Cholera may be mild or severe. Cases have been described in which the infection has been so severe that death has resulted before the classical watery diarrhoea has become established. On the other hand, infection of the intestinal content may be present without causing any clinical signs. In epidemics it is often the case that early and late cases are mild, and those at the height of the epidemic most severe.

The majority of clinically overt cases are severe. Nevertheless, the condition is of short duration, seldom lasting more than five days.

Incubation Period

The incubation period varies from a few hours to five days. Commonly it is about three days. There are no prodromal symptoms.

The Classical Attack

It is usual to describe the development of severe case in three stages, which often merge indistinguishably into one another. These stages are those of (1) evacuation, (2) collapse, and (3) reaction.

The stage of evacuation commences with diarrhoea which may at first be mild, but which soon empties the bowel of faeces and changes to the urgent watery diarrhoea of the classical condition. The patient now passes frequent watery stools which amount to little more than large quantities of clear or slightly opalescent, non-offensive liquid containing practically no faeces. Against a dark background little flecks of mucosa can often be seen floating about. This appearance has led to the descriptive name of 'rice water stools.' The stools swarm with vibrios. In the late stages there may be a little blood.

Bowel motions are frequent, effortless and uncontrolled. Napier refers to them as the painless passage of pints of pale fluid. The stool comes out in spurts, sometimes with considerable force. The general appearance is that of the turning on and off a faucet. There is no pain and no colic, and the patient is often scarcely aware that he is evacuating his bowel. Contamination of bed clothing is therefore frequent unless watched for.

Vomiting begins as a rule shortly after the diarrhoea has started. There is no nausea. The patient has little or no control over the vomitus, which gushes out with considerable force and volume. The watery vomit is essentially similar in appearance and content to the stool, and like the latter contains enormous numbers of vibrios and is highly infective. It constitutes a real danger to the unwary physician.

Evacuation continues for a variable time and frequently persists into the second stage of the disease, that of collapse. This algid stage may be reached in a few hours in acute cases and in one or more days in less severe attacks. Evacuation seldom continues, however, for more than three days. The frequent bowel evacuation and vomiting lead rapidly to tremendous loss of fluid and electrolytes. Within a matter of hours the severely ill patient becomes dehydrated. The whole body seems to shrink; sub-cutaneous fluid is lost and the pale, clammy skin becomes inelastic and stretched over the underlying tissues. The eyes are sunken, the cheeks hollow, the skin tight over the malar prominences. The mouth and tongue are dry; there is extreme thirst; the voice is husky. The patient becomes anxious, foreboding and restless but remains mentally clear. As the dehydration continues, the circulation becomes inefficient. The blood pressures fall, the pulse quickens and may be impalpable at the wrist. The picture now becomes essentially one of dehydration and vascular collapse and closely resembles similar conditions, such as severe heat exhaustion, in which medical shock has developed.

Muscle cramps are common once dehydration has become evident. They are severe and painful,

frequent, of short duration and arise particularly in the legs. The abdominal muscles are affected only in the later stages. The rectal temperature is seldom raised above normal. Skin and oral temperatures are often subnormal.

At the start of the syndrome the urine volume is reduced and there is usually a thin cloud of albumin; as the dehydration proceeds the urinary output diminishes. Even in relatively mild cases there is oliguria. In severe cases there may be complete urinary suppression, which may be only temporary or may pass on to irreversible acute uraemia. The urine has a low electrolyte concentration. It contains albumin and granular tubular casts and may have a high specific gravity and pigment content.

By the time dehydration is manifest the plasma volume is considerably reduced. When vascular collapse supervenes there is a further reduction. The result is an extreme loss of plasma volume which may amount to over half the initial volume and a corresponding concentration of the cellular elements of the blood. The red cell count and haemoglobin concentration rise steadily to a maximum which may be greatly in excess of normal. The viscosity of the blood is increased.

Death is common at this point from the combined effects of dehydration and shock.

The fate of the patient is determined to a considerable extent by the degree and duration of evacuation and collapse, i.e. by the degree and duration of dehydration and vascular failure. If the algid state has lasted only a few hours, the third stage, that of circulatory recovery is commonly followed by rapid return to health. Reaction is ushered in by a rise of blood pressure, slowing and improvement of volume of the pulse, a return of normal coloration to the skin and a rise of body temperature sometimes to above normal and occasionally to hyperpyrexial levels. Evacuation and vomiting, if not already stopped during the stage of collapse, now cease.

If the algid state has been prolonged or very severe, there may be no circulatory recovery or a temporary reaction stage may be followed by serious and sometimes irreversible changes in vital organ function and the threat to life again becomes urgent.

This is particularly so in cases in which anuria has developed in collapse. If the anuria has been of very short duration reaction may be immediately followed by recovery of urinary flow and renal function. On the other hand, however, in some cases, especially those in which the anuria has been prolonged, renal failure may persist into acute uraemia. Such cases usually die within a few days; even in their late stages, however, recovery may occur, as it does in other examples of

the renal anoxia syndrome. Occasionally the anuria of the collapse may be followed by a short period of oliguria in which small volumes of urine containing albumin and casts may be passed; anuria then reappears and the patient dies in a few days in uraemia.

In some cases after brief improvement, the peripheral circulation may fail again and the patient dies of shock. It must be noted that in many fatal cases, the algid stage persists to death and there is no recovery stage at all.

The whole progress of the cholera case is only a matter of a few days at the most. Recovery when it occurs is usually rapid, especially with correct treatment, when it is often remarkable, the dehydrated corpse-like patient visibly swelling into something resembling normality almost while he is being watched.

Course and Prognosis

The so-called stages may completely merge in severe cases. In milder cases there may be an interval of recovery after the algid stage followed in turn by the complications of the reaction stage, especially renal or circulatory failure or both. The very severe case may perish literally in a few hours. This is especially so in children.

Prognosis depends considerably on the length of time elapsing from onset to commencement of treatment. If dehydration is very severe and shock develops, the outlook is bad in the individual subject. The longer the dehydrated patient is left untreated, the worse the prognosis. Prognosis is bad if anuria has already developed and persisted for some hours before treatment.

The recovery rate is high with efficient treatment, except in advanced and shocked patients.

Complications of cholera other than renal failure and shock, are rare. Pneumonia is sometimes described, especially in outbreaks in cold climates, and gangrene of the extremities has been reported in a few neglected cases. There are no sequelae in the recovered case. Once the tissue water-salt balance and plasma volume have been adjusted, return to normal is very fast, usually a matter of a few days.

The death rate in local outbreaks or in epidemics is often very high. For instance, it was about 50 per cent. at the height of the recent outbreak in Egypt. Even under epidemic conditions, however, the death rate of patients treated in hospital, who must be regarded as a highly selected population, is usually not much greater than 10 per cent.

In any outbreak there are many mild cases which recover spontaneously or respond remarkably quickly to treatment, and there are probably many more cases without symptoms, even of mild diarrhoea.

Diagnosis

In an outbreak the clinical diagnosis of the individual case is easy. Doubtful cases must be treated as cholera. Any condition leading to acute dehydration with watery diarrhoea and vomiting may be mistaken for cholera. Cholera and algid pernicious malaria, acute food or chemical poisoning and heat exhaustion are also examples of related clinical pictures.

The diagnosis of an isolated case may be difficult. The presence of vibrios may be confirmed in wet or stained stool preparations. Further identification of the organism is essential. The vibrio can often be isolated by inoculation of specimens of faeces into alkaline peptone water and incubation at 37° C. for six to eight hours. The ordinary faecal organisms are partly inhibited by the alkalinity and the vibrio becomes concentrated at the surface of the medium. Further bacteriological identification is then simplified.

Treatment

Treatment of established cholera is essentially a matter of non-specific measures for restoring the biochemical balance of the body and the plasma volume. Specific measures designed to destroy the vibrios or neutralize hypothetical poisonous products are of secondary importance.

Non-Specific Measures

The fluid and salts lost by evacuation must be replaced as rapidly as possible.

The substances missing are essentially water, sodium and chloride. The loss of sodium exceeds that of chloride. It is possibly for this reason that the use of hypertonic saline is apparently more effective than isotonic saline in the initial stages of treatment. In shocked cases the plasma volume must be restored immediately and for this purpose parenteral plasma injection is probably better than saline.

Treatment of the severe case is a matter of parenteral replacement of fluid and salts. The following details are modified from those followed in the Campbell Hospital in Calcutta:—

Solutions:

(a) Hypertonic saline

Sodium chloride 140 gr. (16 gm.).

Pyrogen-free distilled water 1 pt. (1 l.).

(b) Alkaline saline

Sodium chloride 80 gr. (9.0 gm.).

Sodium bicarbonate 180 gr. (20.5 gm.).

Pyrogen-free distilled water 1 pt. (1 l.).

Method

Intravenous injection of saline is given to all dehydrated or collapsed patients. The first pint of hypertonic saline (a) should be administered immediately the patient is admitted. Subsequent dosage may be calculated by clinical assessment of the degree of dehydration or shock or, if possible, by estimating the specific gravity of the blood, which is raised as the result of prevailing haemo-concentration.

If the systolic pressure is 80 mm. Hg or less, or if the specific gravity of the blood is 1058 to 1060, $1\frac{1}{2}$ pt. of hypertonic saline are needed; specific gravity 1060 to 1062, $2\frac{1}{2}$ pt.; over 1062, 3 pt.

The specific gravity is calculated as follows: Blood is taken from the finger into a pipette. A drop of blood is extruded from the pipette below the surface of the contents of a series of mixtures of glycerin and water of known specific gravity, ranging from 1054 to 1064 and starting from the highest. The specific gravity of the blood is taken as being equal to that of the fluid in which the drop of blood remains suspended where it was discharged.

Shock is counteracted by injecting plasma after the first injection of hypertonic saline.

It may be necessary in the collapsed patient to cut down on the vein. Otherwise the infusion is given through a wide bore needle into the cubital or antecubital vein.

Rate of Administration

The first pint of hypertonic saline is given very quickly, i.e. in about five minutes. The second pint is given more slowly, in about 20 minutes. In a big man it may be necessary to give a further pint in about 30 minutes, but usually after the second pint the rate of administration is slowed to about a pint in four hours.

In the first 24 hours the proportion of hypertonic to isotonic saline given should be about 2:1. Some authors advise continuing the hypertonic saline on the following day in the ratio of 1:2 to isotonic, but this is seldom necessary and in any case the injection of saline must be carried out with caution after the first phase of dehydration has been adjusted.

Acidosis associated with the reduction in fixed base may be counteracted by injection of the alkaline saline or of bicarbonate solution (120 gr. to the pint), but the injection of saline is often in itself sufficient to adjust the electrolyte balance.

Check should be kept on the urinary chloride concentration during treatment. Once the chloride content has been re-established, hypotonic saline may be substituted for isotonic. The hypotonic saline is made up by mixing isotonic saline and isotonic glucose in the proportion of 1:1 or 1:2.

Infusion of fluid usually brings about rapid recovery within a few hours. It is seldom necessary to continue it for more than 24 hours, but in cases in which evacuation or shock persist or reappear it may be necessary to continue longer or repeat.

One of the difficulties encountered in parenteral treatment is the development of rigors arising from pyrogens in the solutions used. It may be necessary to stop the infusion temporarily during rigors. Cases which originally present with slight fever are more prone to pyrogenic reactions. These may often be the only sign of fever during the attack. Infusion of saline must not be excessive. An input/output account of fluid should be kept in all patients, and after dehydration has been adjusted the balance should be kept. It may be fatal to overload the patient with fluid, especially if he is anuric.

Specific Treatment

Destruction of the vibrio can be effected to some extent by the use of specific bacteriophage or sulphonamides. Other methods have been recommended from time to time with indifferent success. There is considerable doubt about the efficacy of phage. At present the best approach to specific treatment seems to be the use of the relatively insoluble sulphonamides, such as sulphaguanidine, given in large doses corresponding to those administered in bacillary dysentery. Drug therapy must always be combined with the non-specific therapy detailed above.

Dosage

0.10 gm. per kilo. body weight given immediately. Follow by 0.05 gm. per kilo. body weight every four hours. The difficulty may be to administer the drug against the tide of vomiting.

Symptomatic Treatment

Infusion of saline will usually bring about immense relief in all symptoms including muscle cramps, which may be very violent. Severe pain may be relieved by self-administered chloroform on a handkerchief. Most authors advise against the use of morphia. Atropine, $1/75$ gr., is sometimes recommended in the early stages. The patient should be persuaded to take fluid by mouth if possible. Such fluid should contain glucose. Careful nursing is essential. In the convalescent stage the patient must be kept quiet to avoid the recurrence of vascular collapse.

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