

HIGH EDUCATIONAL INSTITUTIONAL OF UKRAINE  
“Ukrainian medical dental academy”  
Chair of hospital paediatrics’ & children’s diseases

Approved  
at sub-faculty meeting

\_\_\_\_\_

“ \_\_\_\_\_ ”  
\_\_\_\_\_

minutes № \_\_\_\_\_

Chief of the Chair

MD, prof. Kryuchko T. O.

**METHODICAL RECOMMENDATION  
FOR PRACTICAL TRAINING  
FOR STUDENTS V COURSE  
MEDICAL FACULTY**

***Topic: Diphtheria at children. Peculiarity epidemiology and disease incidence at present time. Pathogenesis of local and general manifestation of diphtheria. Classification of clinical forms. Clinical of different form diphtheria depending on age of child, presence prevented vaccinations.***

DIPHTHERIA

Etiology :

Corynebacterium diphtheriae (Gram positive bacteria). The organism produces exotoxin that causes toxic and degenerative changes in viscera and CNS.

Mode of transmission:

By droplet infection or contaminated articles.

Clinical picture :

Incubation period ; 2-7 days.

Age: 6 months - 5 years (less than 6 months is protected by maternal immunity).

Clinical Presentations of Diphtheria :

1. Pharyngeal Diphtheria : The patient is complaining of:

- i. Mild sore throat.
- ii. Moderate fever (but the patient looks very toxic and ill disproportionate to the degree of rise of the temperature).
- iii. Dysphagia, headache, and offensive odour from the mouth.
- iv. The tonsils are congested, swollen with a membrane covering the tonsils and spreading to uvula and anterior pillars. The membrane may be white or dirty grayish in colour (depending on the number of RBCs involved in it). The membrane is adherent and if scrapped off, bleeding occurs which helps toxin absorption, thus it is contraindicated to remove the membrane in any suspected case.
- v. The cervical lymph nodes enlarge with edema of the surrounding tissues leading to bull neck appearance.

2. Laryngeal Diphtheria :

2/3 of cases are secondary to pharyngeal diphtheria, and the remaining 1/3 are primary. The patient is complaining of hoarseness of voice or even aphonia, fever and marked toxicity. Stridor which may result in cyanosis and respiratory obstruction and suffocation.

3. Nasal Diphtheria

The patient suffers from serosanguinous discharge that excoriates the upper lip. This type of diphtheria is a potent source of infection to others.

4. Cutaneous, vaginal or wound lesions: with ulceration and membrane formation.

5. Other rare sites of infection by diphtheria include : vulva, conjunctiva, lips and face.

Complications of Diphtheria :

1. In the first week:

Circulatory collapse due to toxemia.

Respiratory complications:

Laryngeal obstruction by a membrane, atelectasis, bronchopneumonia.

2. In the second week:

Toxic myocarditis: manifested clinically as tachycardia, arrhythmia, heart failure, conductive disorders as heart block.

3. In the third week:

Paralysis of the soft palate manifested by nasal regurgitation of fluids, nasal larynx of voice, loss of movements of uvula and loss of gag reflex.

4. In the 5th and 6th week:

Paralysis of extraocular muscles (manifested by squint which is usually internal due to paralysis of the abducent nerve) and paralysis of intraocular muscles (manifested by loss of accommodation to near vision).

5. In the 7th week:

- i. Vagal neuritis which may result in heart failure or ventricular fibrillation and sudden death. Also, dysphagia, choking and aspiration pneumonia is produced by vagal neuritis. Affection of the recurrent laryngeal branch of the vagus leads to aphonia, stridor, and suffocation.
- ii. Paralysis of the phrenic nerve : diaphragmatic paralysis and respiratory distress

6. In the 12th week:

Peripheral neuritis: affecting the nerves supplying the extremities, trunk and neck. The paralysis is sensory and motor. The paralysis is lower motor neurone in type but differs from poliomyelitis in being bilateral and symmetrical with tender calf muscles and "glove and stocking hypesthesia". Complete recovery is the rule.

Laboratory findings:

Normal or slightly increased WBCs in blood count.

Swab from the membrane will reveal the organism (by Oram stain).

Culture on Löffler's serum is positive.

Urine shows albuminuria and hyaline casts.

ECG (arrhythmia or T wave changes in toxic myocarditis).

Prevention :

1. Active immunization by DPT vaccine : see immunization.
2. Isolation of the patient.
3. Care of contacts: a culture from the nasopharynx must be done to all contacts. If the culture is negative, give the vaccine. If positive give the antitoxin, isolate and give antibiotics till 2-3 successive cultures are negative.

Treatment is usually in hospital

General:

1. Bed rest is obligatory in the first 3-4 weeks for fear of heart failure.
2. Good diet.

Specific :

1. Antitoxin: as early as possible 10,000-100,000 units IM or IV (after doing a sensitivity test)
2. Antibiotics: to kill the organism. Penicillin, erythromycin, cefotaxime are effective. The end point of therapy is three consecutive negative cultures

Pathogenic: glucocorticoids, infusion treatment, interferon.

Complications

1. Myocarditis: oxygen, diuretics, digoxin (in small dose under supervision for fear of toxicity).

2. Circulatory failure plasma or blood transfusion.

3. Neuritis: Splinting of the limbs, physiotherapy and artificial ventilation may be needed

Immunization is necessary following recovery of the patient. At least half of the patients who recover from diphtheria do not develop adequate immunity and remain liable to reinfection.

#### IMMUNIZATION

In diphtheria :

i. Contacts, non-immunized and below 10 years old : are given antitoxin (100,000 units).

ii. Previously immunized contacts: give a booster dose of the toxoid.

iii. Contacts, non immunized and older than 10 years: should be examined daily for the disease and actively immunized (toxoid) later on.

D.P.T.:

Diphtheria (toxoid), tetanus (toxoid) and pertussis (killed organism) are used in combination to decrease the number of injections and to increase the immune response by adjuvant effect. Side effects:

These side effects are caused by pertussis component.

I. Mild side effects:

Local swelling and local tenderness.

Fever which may reach 40°C.

These side effects disappear in few days.

2. Moderate side effects :

Protracted cry and shock like state.

3. Severe side effects:

Febrile convulsions, encephalopathy.

Rarely, brain damage.

***Topic: Diphtheria at children. Methods of laboratory diagnostic (bacterioscopic, bacteriological, serological). Classification of exseptions of diphtheria. Differential diagnosis, complications of diphtheria, principles of treatment and prophylactic.***

Plan of classis.

1. DIAGNOSIS
2. DIFFERENTIAL DIAGNOSIS
3. COMPLICATIONS
4. PROGNOSIS
5. IMMUNITY
6. TREATMENT
7. ISOLATION AND QUARANTINE
8. PREVENTIVE MEASURES

#### DIAGNOSIS

An early diagnosis of diphtheria is essential because delay of administration of antitoxin may impose a serious and preventable risk to the patient. Accurate bacteriologic confirmation by means of

culture requires special media, a proficient laboratory, and a minimum of 15 to 20 hours; smears are not reliable. Consequently, the initial diagnosis, as a basis for therapy, must be made on clinical grounds alone.

The diagnosis of diphtheria is confirmed by the demonstration of diphtheria bacilli cultured from material obtained from the site of infection. Care should be exercised in obtaining the culture. The swab should be rubbed firmly over the lesion or, if possible, should be inserted beneath the membrane; if it can be obtained, a fragment of the membrane should be submitted for culture. Swabs should be taken from the nasopharynx and from any wounds or other skin lesions in patients with suspected diphtheria. Lesions should be cleaned with sterile normal saline, crusted material removed, and the swab applied firmly to the base of the lesion. The physician must notify the laboratory that diphtheria is suspected to have correct media used. If swabs must be shipped to a reference laboratory, a transport medium such as that containing silica gel should be used. A blood agar plate and a tellurite plate should be streaked with the swab. The plates should be placed in the incubator at 37° C without delay. After incubation for 24 to 48 hours, the organisms on the plates should be identified by an experienced laboratorian.

Diphtheria bacilli that are isolated on culture should be classified by biotype (*mitis*, *gravis*, *intermedius*, or *belfanti*) and tested for toxigenicity. Although the original assays for toxigenicity were performed *in vivo*, the method now most commonly used for determining toxigenicity is the Elek immunoprecipitation test. Because diphtheria has become a rare diagnosis in most developed countries, many laboratories are not proficient in performing the test, and specimens will need to be forwarded to a reference laboratory for toxigenicity testing. A polymerase chain reaction (PCR) assay detecting the A and B subunit of the tox gene, which correlates well with the Elek test, has also been developed. The PCR assay may be performed directly on clinical specimens, allowing rapid confirmation of the presence of toxigenic *Corynebacterium* organisms.

#### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of diphtheria varies with the particular anatomic site of involvement. The presentation of nasal diphtheria may be clinically indistinguishable from that of a foreign body in the nose. Tonsillar and pharyngeal diphtheria may resemble streptococcal infection; coinfection with both toxigenic *C. diphtheriae* and group A streptococcus is well documented. Other diagnoses that may be considered in patients with diphtheria of these sites are infectious mononucleosis, nonbacterial membranous tonsillitis, primary herpetic tonsillitis, and thrush. Laryngeal diphtheria may present with signs and symptoms resembling laryngotracheitis or epiglottitis.

#### COMPLICATIONS

The most common and most serious complications are those caused by the effect of the toxin on the heart and central nervous system.

##### Myocarditis

Myocarditis occurs frequently as a complication of severe diphtheria, but it may also follow milder forms of the disease. The more extensive the local lesion is and the more delayed the institution of antitoxin therapy is, the more frequently myocarditis occurs. In most instances the cardiac manifestations appear during the second week of the disease. Occasionally, myocarditis may be noted as early as the first week and as late as the sixth week of the disease. Abnormal electrocardiographic findings include flattening and inversion of T waves; elevation of the ST segment; and conduction abnormalities, including complete heart block. Myocarditis may be followed by cardiac failure.

##### Neuritis

Neuritis also is generally a complication of severe diphtheria. The manifestations of neuritis appear after a variable latent period, are predominantly bilateral, and usually resolve completely. Neuropathy affecting cranial nerves typically occurs early in the course of illness, during the first 4 weeks after the onset of disease; peripheral neuropathy occurs later, 5 to 8 weeks after onset of disease. Cranial nerve involvement rarely if ever occurs as a complication of cutaneous diphtheria without respiratory involvement. Paralysis of the limbs has been reported following cutaneous infection, and the latent period may be quite prolonged.

#### Paralysis of the soft palate.

Soft palate paralysis is the most common manifestation of diphtheritic neuritis. It may occur as early as the first week after onset of illness. It is characterized by a nasal quality to the voice and nasal regurgitation. The paralysis usually subsides completely within 1 to 2 weeks.

#### Ocular palsy.

This palsy usually occurs between the third and fifth week and is characterized by paralysis of the muscles of accommodation, causing blurring of vision. Less commonly there may be involvement of the extraocular muscles, causing strabismus. Involvement of the lateral rectus muscle, causing an internal squint, may also occur.

#### Paralysis of diaphragm.

Paralysis of the diaphragm may occur between the fifth and seventh week as a result of neuritis of the phrenic nerve. Death occurs if mechanical respiratory support is not provided.

#### Paralysis of limbs.

Limb paralysis may occur between the fifth and tenth week. Both sensory and motor nerves are involved. Paresthesias are followed by weakness of the extremities and loss of deep tendon reflexes. Nerve conduction studies show slowing of conduction; prolongation of distal motor latency; and, in severe cases, conduction block. The absence of deep tendon reflexes, bilateral symmetric involvement, and the presence of an elevated level of spinal fluid protein make this complication clinically indistinguishable from the Guillain-Barré syndrome.

#### Other Complications

In severe diphtheria, thrombocytopenia and coagulation abnormalities are not uncommon. The peripheral blood smear may show evidence of microangiopathic hemolytic anemia, and frank disseminated intravascular coagulation may occur. These abnormalities are thought to be a result of the effects of diphtheria toxin on the vascular endothelium. Likewise, proteinuria is commonly found in severe disease, and renal failure may occur.

#### PROGNOSIS

Before the turn of the century the mortality rate of diphtheria was 30% to 50%. The advent of diphtheria antitoxin in 1894 and the beginning of large-scale active immunization programs in 1922 led to a dramatic reduction in the mortality rate to approximately 10%. In spite of subsequent improvements in the care of critically ill patients, case-fatality ratios of 5% to 10% have been reported in most series. Extensive disease and delays in seeking medical care, diagnosis, and receipt of diphtheria antitoxin are risk factors for death resulting from diphtheria. Mortality rates are consistently lower for cases receiving antitoxin within the first 2 days of illness. The susceptibility of the patient is also critical; illness is usually mild in vaccinated persons.

The prognosis in the individual case of diphtheria must be guarded. Sudden death may be caused by a variety of unpredictable events, including the sudden complete obstruction of the airway by a detached piece of membrane, the development of myocarditis and heart failure, or the late occurrence of respiratory paralysis caused by phrenic nerve involvement. Patients who survive myocarditis or neuritis generally recover completely. Occasionally, however, diphtheritic myocarditis may be followed by permanent damage to the heart.

#### IMMUNITY

Antibody to diphtheria toxin (antitoxin) confers protection from severe clinical manifestations of diphtheria. Antitoxin levels of 0.01 to 0.09 IU (international unit)/ml are thought to confer some protection, and with levels of  $\geq 0.1$  IU/ml, protection is considered reliable. However, persons with "protective" levels of antitoxin have developed diphtheria ( Ipsen, 1946 ). Antibodies to other components of *C. diphtheriae* may also play a role in immunity.

Antitoxin levels are most commonly measured by in vitro neutralization in tissue culture. Both enzyme-linked immunosorbent assays (ELISA) and passive hemagglutination have been used, but both are unreliable at low concentrations of antitoxin ( $<0.1$  IU/ml). The poor correlation between results of ELISA and in vitro neutralization at low antitoxin concentrations is thought to be caused by the binding of nonneutralizing antibodies.

#### Passive Immunity

Passive immunity may be acquired either by transplacental transfer of antibody from an immune mother or by parenteral administration of diphtheria antitoxin. Congenitally acquired passive immunity persists for approximately 6 months. Protection after injection of diphtheria antitoxin disappears after 2 to 3 weeks.

#### Active Immunity

Active immunity may be induced either by previous infection with *C. diphtheriae* or, more commonly today, by vaccination with diphtheria toxoid. The toxin is more toxic than immunogenic; thus, reliable immunity is produced only by vaccination. Persons with diphtheria should therefore be immunized. Recurrent attacks of the disease frequently occurred in the prevaccine era, but by late adolescence most of those persons were immune.

Immunization with diphtheria toxoid can be relied on to prevent serious or fatal disease. The widespread and routine immunization of infants and children has had a profound effect on the immune status of the population at large. Fully immunized individuals have antibody to toxin but do not have antibody to the organism and may become nasopharyngeal carriers or, uncommonly, may develop mild disease.

### TREATMENT

#### Antitoxin Therapy

Diphtheria antitoxin must be given promptly and in adequate dosage ( Table 6–1 ). Any delay increases the possibility that myocarditis, neuritis, or death may occur. During an infection, diphtheria toxin may be present in three forms: (1) circulating or unbound; (2) bound to the cells; or (3) internalized in cytoplasm. Antitoxin will neutralize circulating toxin and may affect bound toxin but will not affect internalized toxin. Because bacteriologic confirmation of the diagnosis cannot be obtained immediately, the decision to administer diphtheria antitoxin must be made on clinical and epidemiologic grounds.

Currently available diphtheria antitoxin is of equine origin, and, like any heterologous serum, its administration may be followed by an immediate reaction, such as acute anaphylactic shock, or a delayed type of reaction, such as serum sickness. Any history regarding previous horse serum injections or possible allergy should be obtained before administering the product, and the patient must be tested for hypersensitivity by skin or eye tests. When testing for hypersensitivity or administering diphtheria antitoxin, health-care workers should always have a syringe loaded with a

TABLE 6-1 -- Dosage of Antitoxin Recommended for Treatment of Diphtheria

| Type of diphtheria  | Dosage (units) |
|---|----------------|
| Anterior nasal  | 10,000–20,000  |
| Tonsillar   | 15,000–25,000  |
| Pharyngeal =48 hr duration  | 20,000–40,000  |
| Laryngeal =48 hr duration   | 20,000–40,000  |
| Nasopharyngeal  | 40,000–60,000  |
| Extensive disease of =3 days duration or any patient with brawny swelling of the neck | 80,000–120,000 |

1:1,000 solution of epinephrine ready and available for emergency use.

#### Skin test.

An injection of 0.1 ml of a 1:100 dilution of diphtheria antitoxin in physiologic saline solution is given intracutaneously. The test is read in 20 minutes and is positive if a wheal 1 cm or more in diameter is present. In persons with a history of allergy to equine serum the dose should be reduced to 0.05 ml of a 1:1,000 dilution intracutaneously. The use of undiluted antitoxin will invariably cause a false-positive reaction; dilution is therefore mandatory. A negative skin test does not preclude the occurrence of serum reactions.

#### Conjunctival test.

One drop of a 1:10 dilution of the serum in physiologic saline solution is instilled inside the lower lid of one eye; 1 drop of physiologic saline solution is used as a control for the other eye. The test is read in 20 minutes and is positive if conjunctivitis and lacrimation are present. If a positive reaction occurs, the eye should be treated with 1 drop of a 1:100 solution of epinephrine.

If the history and sensitivity tests are negative, the total recommended dose of antitoxin should be given without delay. The precise dose and route of administration of antitoxin is determined by the location and extent of the membrane, the degree of toxemia, and the duration of the illness. Dosage does

not vary by the patient's age and weight. The dosages shown in Table 6-1 are recommended for the various types of diphtheria.

To neutralize toxin as rapidly as possible, the preferred route of administration is intravenous; antitoxin may also be administered by intramuscular injection, but peak antitoxin levels may not be reached for several days. If intravenous therapy is indicated, antitoxin should be diluted in 500 ml of saline and administered by intravenous drip. The rate should be very slow over the first half hour to allow for desensitization; the entire dose should be administered within 90 minutes. The patient must be carefully monitored, and the infusion must be stopped if signs of shock appear. The addition of 0.1 to 0.3 ml of 1:1,000 dilution of epinephrine to the solution is a useful precaution. If administered by intramuscular injection, antitoxin is injected undiluted into the buttocks.

If a patient is sensitive to horse serum, the indications for the diphtheria antitoxin should be reevaluated because of this potential risk. If the antitoxin is indicated, it can be given following desensitization by the intravenous, intradermal, subcutaneous, or intramuscular regimen, as described in Tables 6-2 and 6-3. Signs of acute anaphylaxis call for the immediate intravenous injection of 0.2 to 0.5 ml of 1:1,000 epinephrine solution.

In the United States, diphtheria antitoxin is no longer commercially available, but it is available from the Centers for Disease Control and Prevention as an investigational agent. Physicians caring for patients with suspected diphtheria should contact their state health department for assistance in obtaining diphtheria antitoxin.

#### Antibacterial Therapy

Penicillin and erythromycin are effective against most strains of diphtheria bacilli. Penicillin is the preferred drug and may be given as aqueous procaine penicillin (25,000 to 50,000 units per kilogram of body weight per day for children, with a maximum dosage of 1.2 million units per day, in two divided doses). Patients who are sensitive to penicillin should be given parenteral erythromycin in a daily dosage of 40 to 50 mg per kilogram, with a maximum dosage of 2 g per day. When the patient can swallow comfortably, oral erythromycin in four divided doses or oral penicillin V (125 to 250 mg four times daily) may be substituted for a recommended total treatment period of 14 days. Antimicrobial therapy is not a substitute for antitoxin treatment.

Eradication of the organism should be documented by culture. Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional 10-day course of erythromycin, and follow-up cultures should be obtained.

TABLE 6-2 -- Desensitization to Serum: Intravenous Route

| Dose number* | Dilution of serum in isotonic sodium chloride | Amount of injection (mL) |
|--------------|---|--------------------------|
| 1            | 1:1,000                                       | 0.1                      |
| 2            | 1:1,000                                       | 0.3                      |
| 3            | 1:1,000                                       | 0.6                      |
| 4            | 1:100   | 0.1                      |
| 5            | 1:100   | 0.3                      |
| 6            | 1:100   | 0.6                      |
| 7            | 1:10  | 0.1                      |
| 8            | 1:10  | 0.3                      |
| 9            | 1:10  | 0.6                      |
| 10           | Undiluted                                     | 0.1                      |
| 11           | Undiluted                                     | 0.3                      |
| 12           | Undiluted                                     | 0.6                      |
| 13           | Undiluted                                     | 1.0                      |

From American Academy of Pediatrics. Passive immunization. In Pickering LK (ed). 2000 Red Book: Report of the Committee on Infectious Diseases, ed 25. Elk Grove Village, Ill: American Academy of Pediatrics, 2000.

\* Administer consistently at 15-minute intervals.

TABLE 6-3 -- Desensitization to Serum: Intradermal (ID), Subcutaneous (SC), and Intramuscular (IM) Routes

| Dose number* | Route of administration | Dilution of serum in isotonic sodium chloride | Amount of injection (mL) |
|--------------|-------------------------|---|--------------------------|
| 1            | ID                      | 1:1,000                                       | 0.1                      |
| 2            | ID                      | 1:1,000                                       | 0.3                      |
| 3            | SC                      | 1:1,000                                       | 0.6                      |
| 4            | SC                      | 1:100   | 0.1                      |
| 5            | SC                      | 1:100   | 0.3                      |
| 6            | SC                      | 1:100   | 0.6                      |
| 7            | SC                      | 1:10  | 0.1                      |
| 8            | SC                      | 1:10  | 0.3                      |
| 9            | SC                      | 1:10  | 0.6                      |
| 10           | SC                      | Undiluted                                     | 0.1                      |
| 11           | SC                      | Undiluted                                     | 0.3                      |
| 12           | IM                      | Undiluted                                     | 0.6                      |
| 13           | IM                      | Undiluted                                     | 1.0                      |

From American Academy of Pediatrics. Passive immunization. In Pickering LK (ed). 2000 Red Book: Report of the Committee on Infectious Diseases, ed 25. Elk Grove Village, Ill: American Academy of Pediatrics, 2000.

\* Administer consistently at 15-minute intervals

#### Supportive Treatment

Bed rest is more important in the management of diphtheria than in most other infectious diseases. It should be enforced for at least 12 days because of the possibility of complicating myocarditis. The patient's activity subsequently is guided by the results of the daily physical examinations, the serial electrocardiograms, and the presence or absence of complications. In addition to requiring antitoxin, penicillin, and other supportive measures, patients with laryngeal diphtheria may require treatment for the relief of airway obstruction. Intubation and/or tracheostomy may be necessary. Steroid therapy did not prevent myocarditis or neuritis in one controlled trial ( Thisyakorn et al., 1984 ).

#### Treatment of Complications

Myocarditis and neuritis are the most important complications requiring therapy. In general the management of diphtheritic myocarditis and its sequelae is the same as that used for any other type of acute myocardial damage. Bed rest and inactivity may be beneficial. Sudden death caused by myocardial failure may be precipitated by excessive activity. The administration of digoxin is controversial; however, it should not be withheld if there is evidence of cardiac decompensation. Conduction abnormalities may require use of a temporary pacemaker.

Palatal and pharyngeal paralysis may be complicated by aspiration because of the tendency for regurgitation and difficulty in swallowing. Under these circumstances, gastric or duodenal intubation is indicated. Mechanical ventilation may be required in patients with paralysis of the diaphragm resulting from phrenic nerve involvement.

#### Treatment of Diphtheria Carriers

A carrier is an individual who has no symptoms and harbors virulent diphtheria bacilli in the nasopharynx. The eradication of these microorganisms may be extremely difficult. A single dose of intramuscular benzathine penicillin G (600,000 units for children <6 years of age) or a 7- to 10-day course of oral erythromycin (40 mg/kg/day for children, 1 g/day for adults) is recommended. Although there is some evidence that erythromycin may be more effective in eradicating the carrier state, intramuscular penicillin is preferred if compliance is in doubt. Because neither regimen is 100% effective and bacteriologic relapse may occur, specimens should be obtained for repeated culture a minimum of 14 days after completion of therapy. Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional 10-day course of oral erythromycin, and follow-

up cultures should be obtained ( Farizo et al., 1993 ). Occasionally an undetected foreign body in the nose may be responsible for persistence of a carrier state.

#### ISOLATION AND QUARANTINE

The patient is infective until diphtheria bacilli can be no longer cultured from the site of the infection. Isolation should be maintained until elimination of the organism is demonstrated by negative cultures of two samples obtained at least 24 hours after completion of antimicrobial therapy.

#### Care of Exposed Persons

Close contacts of the patient should be identified, evaluated, and maintained under surveillance for 7 days. Close contacts include household members and other persons with a history of direct contact with a case (e.g., caretakers, relatives, or friends who regularly visit the home), as well as medical staff exposed to oral or respiratory secretions of the case. Both nasal and pharyngeal swabs should be obtained for culture from close contacts, regardless of vaccination status. As soon as specimens are obtained, antimicrobial prophylaxis is recommended, using either a single dose of intramuscular penicillin (600,000 units for children <6 years of age and 1.2 million units for those =6 years of age) or a 7- to 10-day course of oral erythromycin (40 mg/kg/day for children, 1 g/day for adults). If compliance is in question, intramuscular penicillin is preferred.

The diphtheria vaccination status of contacts should be reviewed, and persons who have not been vaccinated should receive an immediate dose of diphtheria toxoid and complete the series in accordance with the recommended schedule for vaccination. In addition, contacts who have not received a booster dose within the last 5 years should receive a booster. If the contact has received diphtheria toxoid within 5 years, no additional vaccine is needed ( Farizo et al., 1993 ).

#### Notification of Public Health Authorities

If the diagnosis of diphtheria is suspected, local or state public health authorities should be notified immediately. Measures to prevent additional cases should be undertaken promptly. In the United States, diphtheria antitoxin is available through state health departments. Notification is mandatory in all states and in most countries.

#### PREVENTIVE MEASURES

The dramatic decline in the incidence of diphtheria since 1922 can be attributed for the most part to mass immunization programs and routine immunization of infants and children. Diphtheria toxoid is prepared by formaldehyde treatment of diphtheria toxin. The limit of flocculation (Lf) content of each toxoid (quantity of toxoid as assessed by flocculation) varies among products. The concentration of diphtheria toxoid used in preparations intended for adult use is reduced because adverse reactions to diphtheria toxoid are directly related to the quantity of antigen and to the age or previous vaccination history of the recipient, and because a smaller dosage of diphtheria toxoid produces an adequate immune response in adults. In the United States, diphtheria toxoid is administered in combination with acellular pertussis vaccine and tetanus toxoids (DTaP) or with tetanus toxoid (DT or Td). Pediatric formulations of diphtheria toxoid (DTaP and DT) are for use among infants and children <7 years of age. Each 0.5-ml dose is formulated to contain 6.7 to 25 Lf units of diphtheria toxoid. Adult formulation diphtheria and tetanus toxoids (Td) is for use among persons =7 years of age; each 0.5-ml dose is formulated to contain =2 Lf units of diphtheria toxoid. The vaccine is administered by intramuscular injection. In infants the anterolateral aspect of the thigh provides the largest muscle mass and is the recommended site for intramuscular injection. In toddlers and older children the deltoid may be used if the muscle mass is adequate.

In the United States the routine diphtheria, tetanus, and pertussis vaccination schedule for children <7 years of age is composed of 5 doses of vaccine containing diphtheria, tetanus, and pertussis antigens. Three doses should be administered during the first year of life, generally at 2, 4, and 6 months of age. The fourth dose is recommended for children 15 to 18 months old to maintain adequate immunity during the preschool years. The fourth dose should be administered at least 6 months after the third. The fifth dose is recommended for children 4 to 6 years of age to confer continued protection against disease during the early elementary school years. A fifth dose is not necessary if the fourth dose in the series is administered on or after the fourth birthday.

For children <7 years of age in whom pertussis vaccine is contraindicated, DT should be used instead of DTaP. To ensure that there is no interference with the response to DT antigens from maternal

antibodies, previously unvaccinated children who receive their first DT dose when <1 year of age should receive a total of 4 doses of DT as the primary series—the first three doses at 4- to 8-week intervals and the fourth dose 6 to 12 months later. If additional doses of pertussis vaccine become contraindicated after the series is begun in the first year of life, DT should be substituted for each of the remaining scheduled DTaP doses. If a child develops acute anaphylaxis following a dose of DTaP, further doses of the vaccine or any of its components should be deferred. Because of the importance of tetanus vaccination, referral to an allergist for evaluation and possible desensitization should be strongly considered.

Unvaccinated children 1 to 6 years of age for whom pertussis vaccine is contraindicated should receive 2 doses of DT 4 to 8 weeks apart, followed by a third dose 6 to 12 months later to complete the primary series. Children who have already received 1 or 2 doses of DT or DTaP after their first birthday and for whom further pertussis vaccine is contraindicated should receive a total of 3 doses of DT (if <7 years of age) or Td (=7 years of age), with the third dose administered 6 to 12 months after the second dose. Children who complete a primary series of DT before their fourth birthday should receive a fifth dose of DT before entering kindergarten or elementary school. This dose is not necessary if the fourth dose was given after the fourth birthday.

Diphtheria infection may not confer immunity; therefore vaccination should be initiated at the time of recovery from the illness, and arrangements should be made to ensure that all doses of a primary series are administered on schedule.

Because immunity induced by both diphtheria and tetanus toxoids wanes with time, booster vaccination with Td is recommended at 10-year intervals throughout life, following administration of a primary series. Administering the first Td booster vaccination at an adolescent immunization visit at 11 to 12 years of age is recommended to increase compliance and thereby reduce the susceptibility of adolescents to tetanus and diphtheria.

#### Control question:

1. What do you know about methods of diagnosis of diphtheria?
2. With what diseases can you conduct differential diagnosis of diphtheria?
3. What do you know about complication of diphtheria?
4. What immunity will patient get after diphtheria?
5. What can you tell about methods of treatment of diphtheria?
6. Tell, please, about of preventive measures.

#### Literature:

1. Krugman's Infectious Diseases of Children 11th edition (September 18, 2003) by Anne Gershon (Editor), Peter Hotez (Editor), Samuel Katz (Editor) By Mosby.
2. Current Diagnosis & Treatment in Infectious Diseases 1st edition: by Walter R. Wilson, W. Lawrence, MD Drew, Nancy K., Phd Henry, Merle A., MD Sande, David A., MD Relman, James M., MD Steckelberg, Julie Louise, MD Gerberding. Publisher: McGraw-Hill/Appleton & Lange (June 22, 2001)
3. Infectious Disease 2nd edition (September 22, 2003) by Jonathan Cohen, William Powderly By Mosby.

***Topic: Dysentery. Etiology. Pathogenesis. Epidemiology. Classification. Clinical at children of different age groups. Diagnostic. Differential diagnosis. Treatment. Diettreatment. Term of isolation illness and contact persons. Prevention.***

Plan of classis.

1. ETIOLOGY
2. EPIDEMIOLOGY.
3. CLINICAL PICTURE
4. DIAGNOSIS
5. DIFFERENTIAL DIAGNOSIS
6. COMPLICATIONS
7. HOSPITAL MANAGEMENT
8. PREVENTION.

**Essentials of Diagnosis**

- Enteritis caused by *Shigella* species may be watery (*Shigella sonnei*, *Shigella boydii*) or dysenteric (*Shigella dysenteriae*, *Shigella flexneri*).
- Risks include ingestion of fecally contaminated food or water and contact with infected individuals.
- Definitive diagnosis requires microbiologic isolation and identification of *Shigella* species or molecular evidence of infection.

**General Considerations**

**Epidemiology.** Dysentery is a disease of antiquity and has been described throughout the ages. It was not until the 19th century that dysentery was recognized to be caused by either parasitic amoebae or certain bacteria. In 1898, Shiga recognized and isolated bacteria from patients with dysentery that would agglutinate when exposed to the patient's serum. Today, the most commonly recognized agents of bacterial dysentery are *Shigella* species and the EIEC.

*Shigella* species are unique among bacterial enteric pathogens in that < 200 and possibly = 10 organisms may transverse the gastric acid barrier and cause disease. For this reason, person-to-person transmission is common. Person-to-person transmission results in increased frequencies of shigellosis in day care centers, schools, and custodial-care facilities. Disease is most common in infants and young children and frequently occurs in family members of patients. Peak incidence occurs in the summertime, and common houseflies are thought to contribute to the spread of disease. Outbreaks have also occurred from fecally contaminated food. Transmission through contaminated water is most common in developing countries that lack adequate sewage and water treatment facilities.

In the United States, *S sonnei* is the most commonly encountered *Shigella* species, whereas *S boydii* has a worldwide distribution. The prevalence of shigellae appears to be cyclic, with replacement of the predominant strain approximately every 20 years. This cycling of prevalence is presumably secondary to slowly acquired herd immunity in a given host population. Epidemic shigellosis, caused by *S dysenteriae* and *S flexneri*, is prevalent in underdeveloped countries, but may develop anywhere that poverty, overcrowding, or conditions of war exist.

**Microbiology.** *Shigella* are nonmotile, facultative anaerobic, gram-negative bacilli that are closely related to the genus *Escherichia*. At least 40 serotypes compose four groups or species. These are *S dysenteriae* (serogroup A), *S flexneri* (serogroup B), *S boydii* (serogroup C), and *S sonnei* (serogroup D).

The numbers of shigellae present in the stool vary with the course of disease. Early in the watery-diarrhea phase, shigellae are abundant and number 10<sup>3</sup>-10<sup>9</sup> shigellae/g of feces. During this phase of disease, shigellae are easily recovered on MacConkey or eosin methylene blue (EMB) agar, where they appear as lactose nonfermenting colonies. Later in the course of disease, in the dysentery and postconvalescent phases, bacterial stool counts decline to 10<sup>2</sup>-10<sup>3</sup> shigellae/g of feces. Furthermore, the recovery of shigellae is inversely proportional to specimen transport time, especially in stool specimens

with a low number of shigellae. During the latter phase of disease, culture is best accomplished by rapid specimen transport or bedside medium inoculation, combined with the use of enrichment broth and moderately to highly selective media, such as xylose-lysine-desoxycholate medium and Shigella-Salmonella medium.

In many laboratories, suspect colonies, lactose nonfermenters, are screened by using a three-tube set:

- (i) one tube containing triple sugar iron (TSI) or Kligler iron agar (KIA),
- (ii) the second containing lysine iron agar (LIA), and
- (iii) the third containing Christensen's urea agar (CU).

On the TSI and KIA, shigellae characteristically produce an alkaline slant and acid butt without the production of gas. Rare isolates may produce gas. Negative reactions are produced on the LIA and CU, because shigellae do not decarboxylate lysine or hydrolyze urea. In addition, shigellae do not produce hydrogen sulfide, which is detected by the TSI, KIA, and LIA systems. An attempt to agglutinate organisms that are thought to represent *Shigella* species may be performed by using group antisera. Isolates with a suggestive screen profile are further characterized by additional biochemical reactions in either traditional or automated systems.

Useful clues in the identification of shigellae include the following: the majority of shigellae cannot ferment mucate, cannot use acetate, and are negative for indole and ortho-nitrophenyl- $\beta$ -galactopyranoside.

**Pathogenesis.** Shigellosis may produce either predominantly watery diarrhea or watery diarrhea that progresses to dysentery. The severity of disease is largely determined by the invading organism. *S. dysenteriae* and *S. flexneri* are the agents most commonly associated with bacillary dysentery, whereas the other *Shigella* species more often produce watery diarrhea.

The pathogenesis of the watery-diarrhea phase of bacillary dysentery is caused by a combination of luminal bacterial replication and superficial mucosal invasion in the small intestine. During this phase of disease, large numbers of shigellae are present in the lumen of the small intestine. This phase of the disease is correlated with the onset of cramping abdominal pain, fever, and toxemia.

Within days, the luminal contents of the small intestine do not contain shigellae, and the site of infection is the colon. The shigellae invade colonic mucosa and occasionally invade to the level of the submucosa. Factors that are important for invasion are present on the bacterial chromosome, as well as on a 140-MDa plasmid. Eventually, epithelial cell death occurs, and the mucosa sloughs, possibly secondarily to shigatoxin production. The loss of mucosa evokes an intense inflammatory response and allows for the introduction of coliform bacteria. Microabscesses, epithelial ulcerations, and pseudomembranes that consist of sloughed epithelial cells, bacteria, fibrin, and inflammatory cells may be seen. This phase of the disease correlates with tenesmus and fractionated stools that contain blood, mucus, and inflammatory debris.

## **Clinical Findings**

### **Signs and Symptoms.**

Early in the course of disease, when bacteria are present in the small intestine, patients develop acute, watery diarrhea; fever; and abdominal pain.

Patients may become toxemic and fever may reach as high as 38-39 °C. Later in the course of disease, the primary site of infection is the colon. In this phase, fever continues, but is usually less pronounced. The pain that is present is usually in the lower abdominal quadrants. Cramping abdominal pain and tenesmus (pain in the rectum during defecation or attempted defecation) are common.

Stools become dysenteric, consisting of a mixture of neutrophils, blood, mucus, and debris. Frequent, small-volume or fractionated stools may occur, and tenesmus is often present, but in some cases of shigellosis, the stools may be initially watery becoming bloody after 1-2 days. Patients experience pain upon rectal examination (sphincterity). Colonoscopy discloses hyperemic and friable-to-ulcerated colonic mucosa.

### Main differences between different types of dehydration

|                     | Isotonic<br>(isonatremic) | Hypertonic<br>(hypernatremic) | Hypotonic (hyponatremic) |
|---------------------|---------------------------|-------------------------------|--------------------------|
| Prevalence          | > 75%                     | 10- 1 5%                      | 5 - 1 0%                 |
| Losses              | water = sodium            | Water > sodium                | Water sodium             |
| Plasma osmolality   | Normal                    | -                             | -                        |
| Serum Na            | N                         | -                             | -                        |
| ECV volume          | --                        | -                             | ---                      |
| ICV volume          | maintained                | ---                           | -                        |
| Thirst              | ++                        | +++                           | ±                        |
| Loss of skin turgor | ++                        | Not lust                      | +++                      |
| Seizures            | may occur                 | common                        | may occur                |
| Mental state        | irritable/lethargic       | very irritable                | Lethargy/coma            |
| Shock               | in severe cases           | uncommon                      | Common                   |

#### I. History Taking:

Ask for:

1. Duration of diarrhoea.
2. Consistency, frequency and volume of stools.
3. Presence of mucus and blood in stools (blood and mucus in the stools, with associated fever, suggest an invasive organism).
4. Presence of fever, vomiting, convulsions or other problems (e.g. cough, discharging ear, etc).
5. Frequency of vomiting and colour of vomitus (coffee ground vomitus occurs in DIG).
6. Type and quantity of fluids, milk and food consumed during the illness.
7. Drugs received.
8. Nutritional history : because :
  - Dietetic errors may cause diarrhoea e.g.: over feeding, food allergy, giving a non, suitable diet as too concentrated formula or a food which is not suitable for age.
  - Also, malnutrition leads to diarrhoea by many factors (infection, mal-digestion, malabsorption or lactose intolerance), so, its management is more difficult than management of diarrhoea in a well nourished infant.
9. Past history of similar attacks (ask for their frequency, duration and response to treatment).
10. Family history of similar condition in other members of the family. Bad living conditions predispose to food contamination by micro-organisms and thus diarrhoea.

#### II. Clinical examination:

General look

- Well and alert.
- or - Irritable and thirsty.
- or - Floppy, lethargic and may be unconscious.

Vital signs:

Pulse:

- Exclude signs of shock: rapid, weak pulse (with cold cyanotic extremities).

Blood pressure:

- Hypotension may be present in severe cases.

Temperature: fever due to the infection and dehydration.

Respiratory rate:

- Rapid deep breathing (in acidosis).
- Rapid shallow (if there is associated pneumonia).

Anthropometric measurements: (weight, length and head circumference).

- To exclude malnutrition.

- Accurate weighing is critical for calculating fluid requirements and assessing the success of rehydration.

#### Head and neck:

- Depressed anterior fontanel (due to dehydration).
- Eyes are sunken with absent tears in dehydration.
- Mucous membranes of the mouth and tongue: dry.
- Exclude presence of infections as otitis media.

#### Extremities:

- Cold cyanotic extremities in shock.
- Wasting of muscles, loss of subcutaneous fat if malnourished.
- Gangrene due to thrombosis of limb vessels (most probably in DIC).

#### Skin:

- Loss of skin elasticity.
- Loss of subcutaneous fat if malnourished.

Chest: Exclude pneumonia,

#### Abdomen:

- Abdominal distension with diminished peristalsis (most probably due to hypokalemia or toxic ileus).

#### CNS:

- Exclude meningitis (revise signs of meningeal irritation).
- Convulsions occur due to :
  1. Hyper or hyponatremia.
  2. Post-acidotic hypocalcemia.
  3. Hypoglycemia particularly in malnourished infants.
  4. Febrile convulsions.
  5. Meningitis or encephalitis by the causative organism.
  6. Disseminated Intravascular Coagulation (DIC) leading to thrombosis or intracranial hemorrhage.
  7. Sinus thrombosis due to severe dehydration leading to brain edema.

### **III. Investigations of Infantile Diarrhoea:**

1. Stool: Stool analysis and culture to detect the causative organism.
2. Serum electrolytes => Na, K.
3. pH and serum bicarbonate (for acid-base balance).
4. Urine analysis to exclude urinary tract infection.
5. If systemic sepsis is suspected: Blood and urine cultures are required.
6. In severe complicated cases:
  - Renal function tests
  - Investigations to exclude DIG (as prothrombin time, partial thrombo-plastin time, platelet count and fibrin degradation products).

Exikosis at children with acute intestine infections

| Indications           | Degree of exikosis |                   |                       |
|-----------------------|--------------------|-------------------|-----------------------|
|                       | I                  | II                | II                    |
| Decrease of weigh (%) | 5-6                | 6-10              | 10-15 and more        |
| Stool                 | not frequent       | to 10 time a day  | Frequent (10-20 time) |
| Vomiting              | 1-2 time           | repeated          | frequent              |
| General state         | middle             | hart              | hart                  |
| Thirst                | moderate           | sharply expressed | can absent            |
| Mucosa membranes      | moist              | dry               | dry, bright           |
| Anterior fontanel     | normal             | depressed         | pulled in             |

| Eyes             | normal                                  | soft  | depressed   |
|------------------|---|---|---|
| Other indication | function of other systems not violation | marbleness of skin, taxycardia, irritability, diuresis decrease | pulls weak (with cold cyanotic extremities), BP decrease, taxycardia, acrocianisis, coma, oliguria (anuria) |

### Differential Diagnosis.

When watery diarrhea predominates, other bacterial, parasitic, and viral enteric pathogens must be considered.

*Entamoeba histolytica* and EIEC must also be considered in patients with dysentery. Infection with *E. histolytica* is most commonly associated with travel to or living in endemic locales. These organisms are readily recognized on a microscopic examination of the stool for ova and parasites. Dysentery caused by the EIEC, however, may pose a diagnostic challenge for the clinical microbiologist. The EIEC, unlike other *E. coli*, are often nonmotile, may not ferment lactose or may ferment it slowly, are lysine decarboxylase negative, and may cross-react with *Shigella* antisera. Laboratory personnel must recognize this potential pitfall and exclude this organism through additional testing (see above).

Noninfectious causes of diarrhea must also be considered. The differential diagnosis of noninfectious colitis is extensive and includes inflammatory-bowel disease, lymphocytic/collagenous colitis, neoplasia, and numerous other disorders. Patients with inflammatory-bowel disease may also have fecal leukocytes, limiting the usefulness of this test. An accurate diagnosis may be achieved through a thorough history and physical examination, excluding enteric pathogens through appropriate microbiologic studies, and by obtaining and reviewing gastrointestinal biopsies via endoscopy and histopathologic studies.

### Complications:

This occurs especially with *Shigella*:

Intestinal perforation; Toxic megacolon; Rectal prolapse; Convulsions; Septicemia; Hemolytic - Uremic syndrome; Prolonged hyponatremia; Malnutrition; Protein-losing enteropathy.

### Diagnosis

Patients with acute diarrhea, which may be watery to dysenteric; fever; abdominal pain; and systemic symptomatology/toxemia may have shigellosis. A history of exposure to individuals with shigellosis, travel to endemic areas, and exposure to a high-risk population, such as persons in a custodial-care facility, should raise the index of suspicion. The presence of leukocytes in the stool, although supportive, is by no means definitive for shigellosis. Fecal leukocytes may be present in the stools of patients with other bacterial enteritides, amoebic dysentery, pseudomembranous colitis, and noninfectious disease, such as inflammatory-bowel disease. The definitive diagnosis requires the microbiologic identification of a *Shigella* species.

*Shigellae* are particularly susceptible to some environmental changes, and they die rapidly in transport. Therefore, it is imperative to rapidly transport the stool of patients suspected of having shigellosis to the laboratory. This is especially important for patients in the latter stages of disease, in whom the number of shigellae in the stool are relatively few.

More than 60% of cases are due to *Shigella*. Amebiasis can only be diagnosed when trophozoites of *E. histolytica* containing RBCs are seen in fresh stools.

Unless *E. histolytica* trophozoites containing RBCs are detected in stools, patients will be treated on the assumption that they have shigellosis.

### Treatment

Treatment includes;

1. Antimicrobial
2. Fluids
3. Feeding

In most instances, this is readily accomplished by oral rehydration. Unlike in many other bacterial enteritides, antibiotic therapy is important in the treatment of shigellosis. Antibiotic therapy limits the clinical course of the disease, may decrease the likelihood of intestinal complications, and decreases the fecal excretion of viable pathogenic organisms, which in turn diminishes transmission. Fluoroquinolones are the treatment of choice for adults. TMP/SMX is the treatment of choice for children. Alternatives are ampicillin, chloramphenicol, and nalidixic acid. In areas of known resistance to TMP/SMX, such as parts of Southeast Asia, Africa, and South America, quinolones should be used for adults, and one of the above mentioned alternatives for children with shigellosis. When available, the antimicrobial-susceptibility profile should guide therapy.

#### Antimicrobial therapy:

- Nalidixic acid 15 mg/kg 4 times /day for 5 days.
- Metronidazole 10 mg/kg 3 times /day for 5-10 days in Amebiasis.
- Ceftriaxone for shigella is very effective: dose = 40 mg/kg/day. I. V. or I.M. divided every 12 hours for 5 days.

#### Treatment of Shigella Gastroenteritis

|                     | Children   | Adults  |
|---------------------|--|---|
| First Choice        | Trimethoprim-sulfamethoxazole (TMP/SMX)<br>• > 1 month: TMP, 10 mg/kg/d, + SMX 50 mg/kg/d orally, divided every 12 h | Ciprofloxacin: 500 mg orally every 12 h (or another quinolone)                          |
| Second Choice       | Ampicillin:<br>• > 1 month: 25 mg/kg every 6 h<br>• 1-4 wk: 25 mg/kg every 8 h<br>• < 1 wk: 25 mg/kg every 12 h      | Ampicillin: 0.5-1 g orally every 6 h or 1-2 g IV every 4-6 h                            |
| Penicillin allergic | TMP/SMX (as above) or Nalidixic acid, 55 mg/kg/day, orally, divided every 4 h  | Trimethoprim-sulfamethoxazole: 160/800 mg orally every 12 h or 3-5 mg/kg IV every 6-8 h |

The recommended duration of therapy for all treatment regimens is 3-5 days

Antimotility agents, such as diphenoxylate, should not be used. The inhibition of diarrhea increases the contact between the intestinal mucosa and the pathogenic organisms and their toxins and may cause more fulminant disease.

Fluid and electrolyte replacements are necessary for patients with dehydration.

#### Management of Diarrhea:

|                             | PLAN A  | PLAN B  | PLAN C   |
|-----------------------------|---|---|--|
| 1. Fluid Therapy :<br>What? | Give more fluids than usual:<br>-Home made fluids<br>-ORS<br>-water<br>-Breast milk | Give ORS  | Give I V fluids<br>- Polyelectrolyte<br>- Ringer's lactate<br>- Pansol |
| How much?                   | Amount<br><2y: 50-100 ml<br>>2y: 100-200 ml<br>after each loose stools              | 75 ml/kg body weight  | 100 ml/kg body weight  |
| How?                        | By:<br>Cup & Spoon<br>Cup alone<br>Dropper<br>Syringe                               | By:<br>Cup & spoon<br>Cup alone<br>Dropper<br>Syringe<br>Nasogastric tube | I.V. in a peripheral vein  |

#### Feeding:

- A. Breast feeding should be continued.
- B. Milk or milk formula: given as usual (alter rehydration).
- C. Soft & semisolid weaning food usually taken by child should be continued after rehydration.

Accordingly, the management of patients should be focused on:

1. Fluid therapy for prevention of dehydration in children with no signs of dehydration and correction of dehydration in dehydrated children.
2. Proper feeding during and after diarrhea.
3. Management of associated problems or complications.

#### I. **Fluid Therapy:**

A. Infants with no signs of dehydration: (PLAN A):

- Give more fluids than usual to prevent dehydration.
- As a guide, give 50-100 ml (for infants less than 2 years) and 100-200 ml (for children >2 years) after each loose stool.
- Types of fluids that may be used :
  - a) Food-based fluids as thick drinks made from cooked rice, soups (may contain cereals, pulses, potatoes, meat or chicken). If possible, add 3 grams of table salt per litre of fluid.
  - b) Sugar-Salt solution containing 3 g salt and 18 g of sugar per litre of water.
  - c) Oral Rehydration Solution.

N.B. Hyperosmolar fluids like very sweet tea, and sweetened commercial fruit drinks should be avoided as they may cause osmotic diarrhea.

- In young infants, the fluid is given by spoon at a rate of one teaspoonful every 1-2 minutes. Do not use feeding bottles.
- If vomiting occurs, the mother should stop giving the fluid for 10 minutes and then restart again at a slower rate.
- Parents should be taught to watch the symptoms of worsening diarrhea, dehydration, or other serious problems including :
  - a) Passage of frequent large watery stools.
  - b) Repeated vomiting.
  - c) Increased thirst.
  - d) Failure to eat or drink normally.
  - e) Fever.
  - f) Blood in the stools.
  - g) No improvement after 3 days.

If such problems appear, child should be immediately brought to the health facility.

#### B. **In infants with mild-moderate dehydration: (PLAN B):**

Oral rehydration therapy (ORS) is the treatment of choice. As a guide, we give 75 ml/kg body weight. However, if a patient is still thirsty or signs of dehydration are still present, more ORS can be given.

- ORS is given by a clean cup and spoon at a rate of 1 teaspoonful/1-2 minutes. Older children can drink frequent sips from the cup directly. (Revise the short account on ORS).
- The amount of ORS is given in 4 hours.
- If the child vomits, wait 10 minutes, then continue giving ORS but more slowly (1 teaspoonful/2-3 minutes).
- If the infant is breast-fed, continue breast feeding during the ORS therapy. If he is not breast-fed give 100-200 ml of clean water during ORS therapy.
- Check the child from time to time and fully reassess him after 4 hours:
  - a. If there are no signs of dehydration, shift to plan A.
  - b. If there is some dehydration, continue plan B.
  - c. If there is frequent watery stools, or signs of severe dehydration, shift to plan C
- If the infant is refusing ORS or vomiting is repeated inspire of giving it more slowly, give ORS by nasogastric tube at a rate of 1 5 ml/kg/hour for 5-6 hours.

#### C. **In infants with severe dehydration: (PLAN C):**

Severely dehydrated children should be rehydrated immediately by intravenous route to avoid death from hypovolemic shock.

Intravenous rehydration is indicated in the following conditions:

- Severe dehydration with or without hypovolemic shock.
- Failure of oral rehydration due to extreme fatigue and inability to drink, stupor, coma, uncontrollable vomiting, severe diarrhea with excessive loss of water in stools.
- Paralytic ileus or DIC.

The fluids used intravenously include: Egyptian I. V. Polyelectrolyte Solution, Ringer's lactate solution, or half normal saline with 5% dextrose.

- The amount of fluid required for rehydration = 100 ml/kg of body weight.
- The rate of I V infusion is as follows :

| Age     | First 30 ml/kg in | Then 70 ml/kg in |
|---------|-------------------|------------------|
| <1 year | 1 hour            | 5 hour           |
| >1 year | 0.5 hour          | 2.5 hour         |

- The patient's progress should be assessed/hour. The signs of a satisfactory response include:
  - Return of a strong radial pulse.
  - Improved level of consciousness and ability to drink
  - Much improved skin turgor.
  - Passage of urine.
- If there is no improvement, increase the total amount and rate of I V fluids should be increased. If the patient improves shift to plan A (if there is no dehydration) or to plan B (if there is some dehydration).

## II Feeding:

- Breast fed babies should continue to receive breast milk as usual.
- Formula fed infants are given as usually prepared.
- Soft and semisolid weaning food that are usually taken by the child should also be continued, better salted to taste (meals include vegetable soup, rice, potatoes, bananas, and cereals).
- Small frequent feedings are better tolerated than less frequent large meals.
- After diarrhea has stopped give one extra meal per day for 2 weeks in normal and for longer period in malnourished child.

It is essential to maintain nutrition during diarrhea, food deficits may result from:

- Increased catabolism due to infection and fever.
- Anorexia and vomiting which usually accompany diarrhea.
- Wrong habits as withholding of food during diarrhea.

Nutrition should be maintained during diarrhea because:

- Despite fecal loss of nutrients, more than 60% of nutrients are absorbed.
- Prolonged starvation can lead to malnutrition especially in borderline cases.

## III. Management of complications:

- DIC is treated by correction of dehydration and acidosis and transfusion of platelets and fresh frozen plasma or fresh blood.
- Shock and prerenal failure are managed by urgent intravascular volume expansion. Follow up of renal function tests after correction of dehydration is essential and management is adjusted accordingly.
- Hypnatremia and hyponatremia : in both conditions, it is safer to correct the dehydration very slowly using an isotonic rehydration fluid. The maintenance and one going losses are given as follows: in hypertonic dehydration : pansol + glucose (2 : 1) and in hypotonic dehydration: pansol + 3% NaCl (2 : 1)
- Post acidotic tetany: this is corrected by slow I.V. infusion of 10% solution of calcium gluconate.
- Post acidotic hypokalemia: It is prevented by simultaneous correction of acidosis and hypokalemia (e.g. by the I.V. polyelectrolyte solution). The correction of hypokalemia should be slow to avoid

cardiac arrhythmias. The I.V. potassium infusion should never exceed one milliequivalent/kg body weight per hour and usually ensure good urine output.

- Hypoglycemia it is treated with I.V. glucose 20%, 2.5 ml/kg given over 5 minutes.

#### **Prognosis**

The prognosis is generally good for patients with endemic or sporadic shigellosis. Infants and the elderly, especially if malnourished, suffer the highest mortality. Epidemic shigellosis caused by *S dysenteriae*, however, is a severe and often life-threatening disease with mortality rates from 5% to 20%. This disease must be treated aggressively with antimicrobial and rehydration therapies.

#### **Prevention & Control**

The development and refinement of sewage disposal and drinking water treatment systems are important in developing countries. In both developed and developing countries, personal hygiene, good hand washing practices, and clean living conditions are important preventive measures, particularly in custodial-care facilities.

#### **Prophylactic Measures**

- Appropriate sewage disposal and waste treatment
- Treatment of drinking water (chlorination)
- Good personal hygiene
- Thorough cooking of food, especially eggs and hamburger
- Good food preparation skills (ie, avoid cross-contamination)
- Bismuth subsalicylate for travelers may aid other prophylactic measures

#### **Isolation Precautions**

- Good handwashing necessary, especially if the infecting organism is *Salmonella typhi*, *Salmonella paratyphi*, *Shigella* spp.
- Patients recovering from enteric fever should not work as food preparers until stool cultures are negative.

Fly control and hygienic food preparation practices should also diminish the incidence of disease.

#### **Literature:**

4. Krugman's Infectious Diseases of Children 11th edition (September 18, 2003) by Anne Gershon (Editor), Peter Hotez (Editor), Samuel Katz (Editor) By Mosby.
5. Current Diagnosis & Treatment in Infectious Diseases 1st edition: by Walter R. Wilson, W. Lawrence, MD Drew, Nancy K., Phd Henry, Merle A., MD Sande, David A., MD Relman, James M., MD Steckelberg, Julie Louise, MD Gerberding. Publisher: McGraw-Hill/Appleton & Lange (June 22, 2001)
6. Infectious Disease 2nd edition (September 22, 2003) by Jonathan Cohen, William Powderly By Mosby.

***Topic: Meningococcal infection. Etiology. Pathogenesis. Epidemiology. Classification. Clinical at children of different age groups. Diagnostic. Differential diagnosis. Treatment. Syndrome of Waterhause-Friderixen. Intensive treatment. Term of isolation illness and contact persons.***

Plan of classis.

9. ETIOLOGY
10. EPIDEMIOLOGY.
11. CLASSIFICATION
12. CLINICAL PICTURE

13. DIAGNOSIS
14. DIFFERENTIAL DIAGNOSIS
15. COMPLICATIONS
16. PRE-HOSPITAL MANAGEMENT
17. HOSPITAL MANAGEMENT
18. PREVENTION.
19. VACCINE.

#### ETIOLOGY

*Neisseria meningitidis* is a gram-negative diplococcus that is often described as biscuit shaped. It is a common commensal organism of the human nasopharynx and has not been isolated from animal or environmental sources. The meningococcus is fastidious, and growth is facilitated in a moist environment at 35-37°C in an atmosphere of 5-10% carbon dioxide. It grows well on several enriched media, including supplemented chocolate agar, Mueller-Hinton agar, blood agar base, and trypticase soy agar. On solid media, colonies are transparent, nonpigmented, and nonhemolytic.

*N. meningitidis* is identified by its ability to ferment glucose and maltose to acid and its inability to ferment sucrose or lactose. Indole and hydrogen sulfide are not formed. The cell wall contains cytochrome oxidase, which results in a positive oxidase test result.

The meningococci have been divided into serogroups based on antigenic differences in their capsular polysaccharides. Although 13 serogroups are currently recognized, groups A, B, C, W135, and Y account for most meningococcal disease. The other serogroups often colonize the nasopharynx but rarely disseminate. Lipooligosaccharides (e.g., endotoxin) and proteins found in the outer membrane complex are also used to serotype meningococcal strains.

*N. meningitidis* doesn't stable in outwardly environment and it perishes very quickly without organisms (under action of sun rises, heat, disinfection solutions, 70% alcohol. At slime from nasopharynx it can be keeps 1-2 hours. *N. meningitidis* deaths at +50°C after 5 minutes or -7-10 °C during 2 hours

#### EPIDEMIOLOGY.

- Ø Source of infection: ill and bearer patients
- Ø Mechanisms of transmission: drop, seldom contact
- Ø Way of transmission: air-drops
- Ø Susceptibility to infection: general
- Ø Index of contagious: 10-15%
- Ø Age structure: 70-80% children till 14 years old, 50% 1-5 years old
- Ø Number of cases some time
- Ø Season: winter-spring
- Ø Periodicity: Duration of high number of cases is 2-4 years, between epidemic space from 5 till 12 years
- Ø Immunity has typospecific character, sometime can be occur the second incident with other type of pathogenic organisms, newborn can have passive immunity from mother
- Ø Mortality 5-14%, in infant till 50%

#### CLASSIFICATION

- Ø Local form (nasopharyngitis, bearing)
- Ø General form (meningococemia, meningitis, meningococcal meningitis, combination of forms)
- Ø Uncommon manifestations of meningococcal disease include endocarditis, purulent pericarditis, pneumonia, septic arthritis, endophthalmitis, mesenteric lymphadenitis, and osteomyelitis
- Ø This infection has several forms of severity (ease, sever, hard, hypertoxic form)

#### CLINICAL PICTURE

1. Incubation period – 1-10 days
2. Nasopharyngitis: fever 38-39°C, weakness, and headache, running nose, pain in pharynx, hyperemia of mucosa membranes. Symptoms of diseases are disappear during 7-10 days
3. Bearing: can be isolation *N. meningitidis* from nasopharynx without inflammation and increase titers of specific antibodies

### EARLY FEATURES

- Leg pain: 5% in those less than 12 months old, increasing to 50-60% in those aged 5-16 years.
  - Thirst: 3.4% in those less than 12 months old, increasing to 12% in those aged 5-16 years.
  - Diarrhoea: 10% in those less than 12 months old, falling to 3-5% in those aged 5-16 years.
  - Abnormal skin colour: 16-20% in all age groups up to 16 years.
  - Breathing difficulty: 16% in those less than 12 months old, falling to 7-12% in those aged 5-16 years.
  - Cold hands and feet: 35-45% in all age groups up to 16 years.
4. Meningococemia: (blood stream infection) is a potentially life-threatening illness. Symptoms may occur abruptly and progress rapidly. Immediate intervention and treatment are usually necessary. Nearly 20 percent of children who develop meningococemia do not survive. While each child may experience symptoms differently, the following are the most common symptoms of meningococemia:
- fever
  - chills
  - sore throat
  - headache
  - aching muscles and joints
  - malaise (not feeling well)
  - exhaustion and weariness
  - rash is red or purple. Small spots develop at first and may occur in groups anywhere on the body. They often grow to become blotchy and look like little bruises. One or two may develop at first but many may then appear in different parts of the body. The spots / blotches do not fade when pressed (unlike many other rashes). Use **the tumbler test**. Place a clear glass (tumbler) firmly on one of the spots or blotches. If the spot / blotch does not fade and you can still see it through the glass, get medical help immediately.
5. Hypertoxic form
- high temperature
  - hemorrhagic rash
  - intoxication syndrome
  - with widespread hematogenous dissemination, the disease rapidly progresses to septic shock characterized by hypotension, DIC, acidosis, adrenal hemorrhage, renal failure, myocardial failure, and coma
  - without treatment the child will die
6. Meningococcal meningitis - an infection of the membranes that surround the brain and spinal cord
- § in infants, symptoms are difficult to pinpoint and may include:
- neck and/or back pain
  - headache
  - nausea and vomiting
  - neck stiffness
- § in children older than one year, symptoms may include:
- irritability
  - sleeping all the time
  - refusing bottle
  - cries when picked up or being held
  - inconsolable crying
  - bulging fontanelle (soft spot on an infants head)
  - behavior changes
- § meningeal symptoms are present

### THE DIAGNOSIS OF MENINGOCOCCAL MENINGITIS AND MENINGOCOCCEMIA

In addition to a complete medical history and physical examination, diagnostic studies for meningococcal meningitis and meningococemia may include:

- § Lumbar puncture (spinal tap). The pressure in the spinal canal and brain can increase, signs of acute bacterial meningitis are present.
- § Definitive diagnosis of meningococcal disease is made by isolation of the organism from a usually sterile body fluid such as blood, CSF, or synovial fluid, skin lesions or rash. Isolation of meningococci from the nasopharynx is not diagnostic for disseminated disease. Blood and CSF are the usual sources of organism isolation.
- § Other laboratory findings may include elevated sedimentation rate and C-reactive protein, leukocytopenia or leukocytosis, thrombocytopenia, proteinuria, and hematuria. Patients with syndrome of DIC have decreased serum concentrations of prothrombin and fibrinogen.

#### DIFFERENTIAL DIAGNOSIS.

- § acute bacterial or viral meningitis,
- § mycoplasma infection,
- § leptospirosis,
- § syphilis,
- § acute hemorrhagic encephalitis,
- § encephalopathies,
- § serum sickness,
- § collagen vascular diseases,
- § Henoch-Schonlein purpura,
- § hemolytic-uremic syndrome,
- § ingestion of various poisons.

#### COMPLICATIONS.

Acute complications are related to the inflammatory changes, vasculitis, DIC, and hypotension of invasive meningococcal disease.

These can include adrenal hemorrhage, arthritis, myocarditis, pneumonia, lung abscess, peritonitis, and renal infarcts. The vasculitis can lead to skin loss with secondary infection, tissue necrosis, and gangrene. Skin sloughing can necessitate the use of skin grafts.

Bone involvement can lead to growth disturbance and late skeletal deformities secondary to epiphyseal avascular necrosis and epiphyseal-metaphyseal defects. Limb amputation has been reported for patients with purpura fulminans.

Meningitis rarely is complicated by subdural effusion or empyema or by brain abscess. Deafness is the most frequent neurologic sequela, but the reported incidence varies from 0-38%.

Other rare sequelae include ataxia, seizures, blindness, cranial nerve palsies, hemiparesis or quadriparesis, and obstructive hydrocephalus.

The late complications of meningococcal disease are thought to be immune complex mediated and become apparent 4-9 days after the onset of illness.

The usual manifestations are arthritis and cutaneous vasculitis. The arthritis is usually monoarticular or oligoarticular. Effusions are usually sterile and respond to nonsteroidal anti-inflammatory agents. Permanent joint deformation is uncommon.

Because most patients with meningococcal meningitis are afebrile by the 7th hospital day, the persistence or recurrence of fever after 5 days of antibiotics warrants an evaluation for immune complex-mediated complications.

#### PRE-HOSPITAL MANAGEMENT

- § Arrange admission - urgent ambulance (03 in Ukraine).
- § Give benzylpenicillin while waiting for the ambulance unless history of immediate penicillin allergy after previous penicillin administration (e.g. difficulty in breathing, collapse, generalised itchy rash). Benzyl penicillin dose 200-300 IU/kg/day
- § Cefotaxime may be used as alternative.
- § In Ukraine levomicetini succinati 25 mg/kg/one time
- § Analgini+papaverini i/m, corticosteroidi to 5-10mg/kg
- § Warn close family contacts that chemoprophylaxis may be required if meningococcal disease is confirmed.

#### HOSPITAL MANAGEMENT

Do not delay treatment in acutely ill patients - start antibiotics and supportive therapy as soon as possible (may require ITU) and investigate afterwards!

Choice of antibiotics in hospital should be guided by local protocols but the following are usually used:

- § Aqueous penicillin G is the drug of choice and should be given in doses of 250,000-300,000 U/kg/24 hr, administered intravenously in six divided doses. Cefotaxime (200 mg/kg/24 hr) and ceftriaxone (100 mg/kg/24 hr) are acceptable alternatives. Chloramphenicol sodium succinate (75-100 mg/kg/24 hr IV in four divided doses) provides effective treatment for patients who are allergic to beta-lactam antibiotics. Therapy is continued for 7-10 days.
- § Cefotaxime or ceftriaxone plus vancomycin as blind treatment of bacterial meningitis is used.
- § Pathogenic treatment
- § Investigations in hospital meningococci are fastidious and samples require careful handling. Close liaison with microbiologist required.
- § Blood culture x3.
- § Blood for PCR (polymerase chain reaction).
- § Serum for serology - initial paired sample (second 2-6 weeks later).
- § Pharyngeal swab (per-nasal if patient unable to cooperate) other swabs as appropriate, stool for virology. State "meningococci?" on form.
- § Lumbar puncture - once patient is stable, and an assessment made to rule out raised intracranial pressure (may need CT scan). Send cerebrospinal fluid for microscopy, culture, glucose, PCR.
- § Aspirate from other sterile sites suspected of being infected (e.g. joints) for microscopy, culture, PCR.
- § Full blood count, electrolytes, renal function tests, liver function tests.

#### PREVENTION.

- § Close contacts of patients with meningococcal disease are at increased risk of infection and should be carefully monitored and brought to medical attention if fever develops.
- § Prophylaxis is indicated as soon as possible for household, daycare, and nursery school contacts.
- § Prophylaxis is also recommended for persons who have had contact with patients' oral secretions.
- § Prophylaxis is not routinely recommended for medical personnel except those with intimate exposure, such as with mouth-to-mouth resuscitation, intubation, or suctioning before antibiotic therapy was begun.
- § Rifampin is given (10 mg/kg; maximum dose, 600 mg) orally every 12 hr for 2 days (total of four doses). The dose is reduced to 5 mg/kg for infants younger than 1 mo. Other effective antimicrobial agents are ciprofloxacin (500 mg orally as a single dose for adults) and ceftriaxone as a single intramuscular dose (125 mg for children < 15 yr and 250 mg for adults).
- § Penicillin does not eradicate nasopharyngeal carriage, and patients treated with penicillin should receive chemoprophylactic antibiotics before hospital discharge.

#### VACCINE.

A quadrivalent vaccine composed of capsular polysaccharide of meningococcal groups A, C, Y, and W135 is licensed in the United States. The vaccine is immunogenic in adults but is unreliable in children younger than 2 yr. The group B polysaccharide is poorly immunogenic in children and adults, and no vaccine is available against this serogroup.

Routine immunization of the United States population is not recommended at this time, but the vaccine is routinely given to all American military recruits.

Immunization is useful to control outbreaks of meningococcal disease of the serogroups represented in the quadrivalent vaccine. It is also recommended for travelers to countries with a high incidence of meningococcal disease.

Immunization of close contacts of individuals with A, C, Y, or W135 disease should be considered, because it has been useful in the prevention of secondary cases. Individuals with anatomic or functional asplenia and those with complement component deficiencies should be immunized.

Polysaccharide-protein conjugate vaccines are being developed for the prevention of meningococcal disease, and subcapsular proteins and detoxified lipooligosaccharides are being investigated as possible vaccines.

At Ukraine vaccination is carried out on epidemic situation occurs.

Literature:

7. Krugman's Infectious Diseases of Children 11th edition (September 18, 2003) by Anne Gershon (Editor), Peter Hotez (Editor), Samuel Katz (Editor) By Mosby.
8. Current Diagnosis & Treatment in Infectious Diseases 1st edition: by Walter R. Wilson, W. Lawrence, MD Drew, Nancy K., Phd Henry, Merle A., MD Sande, David A., MD Relman, James M., MD Steckelberg, Julie Louise, MD Gerberding. Publisher: McGraw-Hill/Appleton & Lange (June 22, 2001)
9. Infectious Disease 2nd edition (September 22, 2003) by Jonathan Cohen, William Powderly By Mosby.