REVIEW ARTICLE

DIPHTHERIA: CURRENT PUBLIC HEALTH CHALLENGE IN UKRAINE AND WORLDWIDE (LITERATURE REVIEW)

10.36740/WLek202101127

Kateryna V. Pikul, Liudmyla M. Syzova, Valentina I. Ilchenko, Irina M. Zvyagolska
UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE

ABSTRACT

The aim: Of the paper is to analyze the current views on diagnosis and management of diphtheria in children.

Materials and methods: The data of scientific literature have been analyzed, using the bibliosemantic method of study.

Conclusions: The specific prophylaxis is recommended to prevent the infection. It has cross-protection against different strains.

KEY WORDS: children, diphtheria, prophylaxis, management

Wiad Lek. 2021;74(1):137-143

INTRODUCTION

The relevance of the topic is determined by the priority and importance of preserving the health of Ukrainian population by improving the current rate of vaccinated individuals against diphtheria. Diphtheria is assigned to one of the dangerous and life-threatening diseases in humans. Immunization is the only means of creating a favorable epidemic situation [1]. Ensuring of non-susceptibility of people to this infection prevents the incidence and spread of diphtheria in the population.

The WHO reports that epidemic situation in diphtheria morbidity has worsened in the world, particularly in Latin America, where a rise in incidence has not been recorded since 1990s [2]. Diphtheria remains a health threat in India, Venezuela, Yemen, Bangladesh (Cox's Bazar), where the intensive growth of the incidence of this infection began in 2017; 80 % of all reported cases of diphtheria in Latin America were registered in Venezuela. Despite vaccination of Venezuela population, in 2018, 1.2 thousand cases of diphtheria were reported, of which more than 80 cases were lethal. In Haiti, about 250 cases were reported, of which 3 cases were lethal; in Colombia, about 10 cases were reported during the same period, which can be related to forced migration of the population from the countries where diphtheria infection cases are recorded [3-6].

The comparison with the post-Soviet countries, for example, in the Republic of Kazakhstan, showed that long-term dynamics for 1990-2012 is characterized by the outbreaks of diphtheria in the period from 1993 to 1998, when local outbreaks with a peak of incidence in 1995 were recorded (1105 cases, including 31 lethal cases) [7].

According to the WHO reports of 2019, Ukraine is threatened with a diphtheria outbreak due to insufficient stock of anatoxin and low rate of vaccinated population in recent years [8]. In the last 9 years, sporadic cases of diphtheria have been reported in Ukraine annually (with the exception of 2017). In 2010-2018, a total of 56 diphtheria patients, including 12 children and 44 adults were registered. No lethal cases have been reported. The first 2 cases of diphtheria were registered in 2018 in the territory of Lugansk region, controlled by Ukraine. In November, 2019, 23 cases of diphtheria were registered, including 5 cases confirmed by laboratory tests: per 1 case among residents of Lugansk, Khmelnytsky, Ternopil, Zakarpatska regions and Kyiv city. 14 presumptive cases of diphtheria were reported among contact persons in Zakarpatska region and one case in Kyiv. The number of reported cases for the period of 2012-2019 increased 4.6 times: from 5 in 2012 to 23 – in 2019 [9]. In 2019, one case was registered in February (Lugansk region) and in August (Khmelnitsky region). The remaining 18 cases were reported in October. In 2019, among the diphtheria patients 19 cases were reported in adults. By localization of the lesion, in the Luhansk region diphtheria of the eye was reported, and in other cases diphtheria of the throat/ tonsils was registered. According to the results of bacteriological examination, *Corynebacterium ulcerans* was reported in one patient from Kiev, in 18 other cases it was *Corynebacterium diphtheriae*.

According to the Public Health Center, as of the end of 2019, 1542650 adults were vaccinated against diphtheria, accounting for 52.3 % of the planned volume [10].

The last epidemic of diphtheria in Ukraine was reported in 1991-1998. During its time, 495 adults died (MOH data for 1999), but according to the Internet resource, the total number was about 700 people, which is probably a picture in the following 2000- and years and infant mortality. According to the Ministry of Health of Ukraine, in 2003 the incidence among adults in Ukraine decreased by 53 %

and constituted the intensive indicator of 0.33, while the infant diphtheria incidence was 0.44 and exceeded the similar values among the adult population by 25 %. At the end of 2003, the overall mortality rate for diphtheria in Ukraine among adults was 0.8 % and 5.7 % among children. Patients died from severe complications of myocarditis, polyneuropathy, infectious-toxic shock, and all of them were hospitalized late and had their last vaccination more than 10 years ago [11].

THE AIM

The aim of the paper is to analyze the current views on diagnosis and management of diphtheria in children.

MATERIALS AND METHODS

The data of scientific literature have been analyzed, using the bibliosemantic method of study.

REVIEW AND DISCUSSION

Diphtheria is the acute infectious disease caused by toxic strains of corynebacteria and characterized by inflammatory process with the formation of fibrinous film at the site of the invasion of the pathogen, the events of general intoxication due to the entry of exotoxin into the blood, resulted in severe complications, leading to infectious-toxic shock, myocarditis, polyneuritis and nephrosis. It is caused by *Corynebacterium diphtheria*, commonly known as the Klebs-Löffler bacillus [12].

Epidemiology. Human carrier of the toxigenic strain is the source of infection [13]. Diphtheria is spread via contact with airborne respiratory droplets, rarely by contaminated objects (houseware, food). Susceptibility is with contagious index of 10-15%, children aged 3-7 years old are most affected. Immunity is unstable. Retrospective data on the incidence of diphtheria in the territory of Ukraine, which was part of the former USSR suggests that the highest incidence of diphtheria was in 1955 – 93.0 per 100000 population, and compared to 1974, it decreased by more than 1162 times due to vaccination and became 0.08 per 100000 population [14].

The features of the **pathogenesis** diphtheria are [15]:

1. Entry of infection is mucous membranes of the oropharynx, nose, larynx and less frequently, eyes, genital organs, wounds, burns.
2. Multiplication of *Corynebacterium*, production of exotoxin and the action of antitoxin (recovery or formation of carriage).
3. Intracellular penetration of the toxin to the body.
4. Fibrinous inflammation (necrosis, stasis, exudation), depending on the form of diphtheria: a) diphtheritic (oropharynx, wound surface); b) croupous (larynx, trachea).
5. Toxinemia (development of toxicosis) and lesions of the adrenal glands, kidneys, cardiovascular system, peripheral nerves.

Classification of diphtheria is shown in Table I.

Complications of diphtheria:

- Early (at the beginning of the second week): nephrotic syndrome, myocarditis, peripheral paralysis of the cranial nerves.
- Late (at the end of the 3-7 weeks): myocarditis, peripheral paralysis of the spinal nerves (polyradiculoneuritis).

Bacterial carriage:

1. Bacterial carriage of reconvalescents.
2. Transitory bacterial carriage (single-time production of *Corynebacterium diphtheriae*).
3. Short-term: up to 2 weeks.
4. Protracted: more than 1 month.
5. Chronic: more than 6 months.

Diagnostic criteria for oropharyngeal diphtheria

Localized: acute onset, unmarked intoxication, low grade fever (38-39 °C), moderate sore throat in swallowing. Moderate cyanotic hyperemia of the tonsils and oropharynx, without clear border, white-yellow, white-gray exudates, do not go beyond the tonsils in the form of isolated spots or coalesced, dense, adherent to surrounding tissues, bleed when removed or scraped, are tending to grow, regional lymph nodes moderately enlarged, not matted together, non-tender.

Extended: acute onset, moderate intoxication, fever of 39 °C and higher, permanent moderate sore throat, cyanotic hyperemia of the mucous membrane of tonsils, oropharynx; swelling of the mucous membranes, exudates extend beyond the tonsils (pillars, posterior wall of the pharynx, uvula), regional lymph nodes are moderately enlarged, somewhat tender palpable.

Toxic: sudden onset, prominent intoxication, fever of 39-40 °C, significantly enlarged lymph nodes, tender, diffuse hyperemia of the mucous membranes and edema of the nasopharynx, tonsils are coalesced, exudates extends beyond the tonsils (mucous membrane of the cheeks, hard palate), nasal tone in the voice, difficulty breathing (wheezing), swelling of the subcutaneous tissue.

Hypertoxic: sudden onset, highly severe intoxication (vomiting, seizures, loss of consciousness), hyperthermia>40 °C predominate over changes in the oropharynx, fulminant development of infectious toxic shock, life expectancy is unfavorable.

Hemorrhagic: along with the signs of toxic stage II-III diphtheria, exudates becomes hemorrhagic (4-5 days), hemorrhages at the sites of injection, bleeding from the mucous membranes and early evidence of myocarditis.

Diagnostic criteria of nasal diphtheria

Gradual onset, intoxication syndrome is minimal or absent, difficulty in nasal breathing, sanioserous discharges, followed by purulent serosanguineous ones, the appearance of excoriations at the entrance of the nose, rhinoscopy reveals erosions, ulcers, sanguineous crusts or dense, adherent white-grey membrane.

Respiratory diphtheria (true croup):

1. Localized diphtheritic croup (laryngeal diphtheria).
2. Extended diphtheritic croup: laryngotracheitis and laryngotracheobronchitis.

Diagnostic criteria of the respiratory diphtheria

Table I. Classification of diphtheria

Mild form	Localized	Patchy oropharyngeal diphtheria, diphtheria of the nose, eye, genitals, ear, skin.
Moderate form	Localized	Membranous oropharyngeal diphtheria, nasopharyngeal diphtheria, localized croup.
	Extended	Oropharyngeal diphtheria, diphtheria of the nose, eye, ear, genitals.
Severe form	Toxic and hypertoxic	Oropharyngeal diphtheria, diphtheria of the nose, eye, genitals, ear, skin. Extended and descending croup.

Stage of croupous cough (following 2-3 days): moderate intoxication, low-grade fever, dry, sometimes barking cough, loud, hoarse voice, gradual increase of clinical symptoms of laryngeal stenosis.

Stenotic stage (following 2 hours to 2-3 days): moderate intoxication, aphonia, silent cough, stenotic breathing (shortness of breath, involvement of auxiliary muscles), hypoxia (cyanosis of the skin and mucous membranes, tachycardia), agitation.

Asphyctic stage: extremely severe condition, anemia, drowsiness, superficial and frequent breathing, reduced retraction of the intercostal spaces, pale gray skin, cyanosis, cold limbs, dilated pupils, no reaction to the surrounding environment, seizures, loss of consciousness, arrhythmia, hypotension, hypothermia, involuntary urination, defecation; death.

Laboratory verification is bacteriological: bacterioscopy of swabs from the oropharynx (on the border of the affected and healthy mucous membrane), nasopharyngeal and pharyngeal swab for culture; serological: AR, PHAT, ELISA.

In terms of differential diagnosis, consider false croup, which is much more common in the pediatric practice [16].

Acute stenosing laryngotracheitis or false croup (ASLT) is a syndrome of a disease characterized by the airway obstruction, also known as croup. ASLT occurs only in childhood, mainly in children under 3 years of age, and then its incidence decreases from 3 to 6 years and from 7 to 14 years. In children under 6 months of age, this condition does not occur. Boys get sick three times more often than girls.

The main causes of ASLT are viruses (20 %), virus in combination with the bacterium (45 %), mycoplasma (15 %), chlamydia (7 %). Among viruses, parainfluenza viruses are responsible for 45 % of cases; other causes include the following viruses: influenza (18 %), adenovirus (13.6 %), respiratory syncytial virus (3 %). In 2005, Human bocavirus (HBoV) was discovered, which causes ASLT in children aged 3 years and is associated with intestinal dysfunction (vomiting, diarrhea). The cause of ASLT is also pediatric infectious diseases: scarlet fever, pertussis and others. In children aged 3 to 7 years, ASLT can be also caused by a newly discovered metapneumovirus, which combines croup syndrome and inspiratory dyspnea in its clinical presentation.

Epithelial tropism is characteristic to all viruses; however, 2 groups of viruses are distinguished on their ability to cause pathological process:

1. Viruses with specific epithelial tropism (parainfluenza, influenza, rhinovirus, respiratory syncytial virus, bocavirus), which cause pathological process with the destruction of epithelial cells and cause gross morphological changes.
2. Viruses, for which epithelial cells are the primary foci of infection on the site of the entry (adenovirus, measles, rubella, herpes simplex virus).

Pathogenesis of croup syndrome involves:

1. Edema of the mucous membrane of the larynx and trachea;
2. Spasm of the larynx and trachea muscles;
3. Hypersecretion of the glands of the airway mucosa.

Pathomorphological alterations are manifested by hyperemia and swelling of the mucous membrane of the larynx and trachea, accumulation of pathological mass and its transformation into the crusts, especially in the hyposecretory form of the disease. During the microscopic examination of the mucosa, dystrophic changes in the epithelium, its desquamation, as well as necrotic-hemorrhagic and fibrinous-necrotic changes are detected, in case of secondary bacterial infection.

Main clinical manifestations: harsh barking cough, inspiratory stridor, hoarseness.

The clinical course of ASLT is staged. Compensated, subcompensated, decompensated and terminal (pre-asphyxia) stages are distinguished. The onset of the disease is sudden, at night, when stridor and dry high-pitched (barking) cough occurs. Overall agitation, restlessness, sleep disorder, loss of appetite occurs; but at the end of the night, the events of laryngeal stenosis disappear and appear again at night, lasting for several days in succession. However, occasionally, the events of laryngeal are growing at the daytime and laryngeal stenosis of I, II, III degree consistently appears. The occurrence of respiratory distress at night can be explained, perhaps, by the fact that due to the horizontal position of the child in the subglottic space, the swelling of the mucous membrane increases and accumulation of pathological mass in the larynx occurs, which contributes to laryngospasm.

Compensated stage is characterized by agitation, cry and sleep disorder. Stridor and inspiratory dyspnea is characteristic; inspiration is prolonged without the pause between inspiration and expiration in case of child's activity. At rest no inspiratory dyspnea occurs, though a marked increase in cardiac activity as a response to inspiratory dyspnea is noted. At this stage, the act of breathing is rearranging,

providing the body with oxygen. Carbon dioxide irritation of the respiratory center is crucial.

Subcompensated stage is characterized by the growing respiratory distress, inspiratory dyspnea is observed at rest, and if the child is agitated, auxiliary muscles are involved in the act of respiration, which is manifested by the suprasternal, intercostal, and subcostal retractions. The events of heart failure are growing. Chest X-ray reveals enhancement of pulmonary pattern, indicating pulmonary circulation disorder.

Decompensated stage is characterized by the prominent respiratory distress. Sternal and *prelum abdominale* muscles are involved in the inspiration and, consequently, epigastric area is significantly retracted. The increased activity of the respiratory muscles contributes to the increased oxygen deficit, resulting in the development of deep acidosis and disorder of redox processes. Suboxidized metabolic products block enzyme systems, lading to worsening of oxygen disposal. Consequently, cyanosis of visible mucous membranes increases and the skin acquires a marble appearance, which is the ominous sign of circulatory collapse. Blood pressure abruptly declines, pulse becomes weak. On auscultation, respiration in the lungs is attenuated and sometimes even not audible that is caused by respiratory distress.

Pre-asphyxia stage is characterized by superficial breathing of Cheyne-Stokes type, pliable areas of the chest and the epigastric area are not retracted, stridor is not audible. Cough is also not audible. The heart tones are muffled, pulse is almost absent, blood pressure is not determined. Cyanosis is changing to sharp paleness, the patient is unconscious, the pupils are dilated, enophthalmia is observed, involuntary urination and defecation. Untimely medical care can lead to death due to impairment of tissue respiration, caused by hypercarbia, intoxication.

Clinical forms of false croup:

1. Edematic form is characterized by growing severity, unproductive dry barking cough and hoarseness. Forced position of the body in children above 2 years of age is characteristic. On auscultation, respiration in the lungs is attenuated;
2. Spasmodic form is characterized by stridor. During sleep, breathing is smooth, calm; loss of voice occurs upon wake up. Minor or no auscultatory changes;
3. Hypersecretory form is characterized by the cough with viscous sputum, the health state is worsening during sleep due to obturation that causes laryngospasm;
4. Mixed form.

Croup severity assessment on clinical manifestations:

1. Suprasternal retraction, signs of Type I respiratory failure, oxygen saturation is 90 %;
2. Perioral cyanosis, respiratory rate is by 25 % higher the age norm, intercostal retraction, Type II respiratory failure, oxygen saturation is 90 %-70 %. The child requires intensive care;
3. Acrocyanosis, sternal retraction, respiratory rate is by 50 % higher the age norm; oxygen saturation is lower than 70%, Type III respiratory failure. The patient should be transferred to the intensive care unit;
4. Asphyxia, total cyanosis, terminal state of health, arrhythmic respiration, jugular venous distention, respiratory rate is by 70 % higher the age norm, oxygen saturation is lower 50 %.

ASLT should be differentiated from **laryngeal diphtheria (true croup)**, which is characterized by a slow onset, hoarseness, fibrinous membranes, growing respiratory distress. The events of toxicosis, cervical lymphadenitis and edema of tissues are observed. From the very beginning, a productive, but not a dry cough appears; it becomes dry after formation of the membranes. In laryngeal diphtheria aphonia is the hallmark. Finally, findings of bacteriological study are crucial.

Staging is characteristic feature of the progress of laryngeal diphtheria: catarrhal or dysphonic (croupy cough), stenotic (compensated, subcompensated and decompensated) and asphyxial. The initial stage lasts for 1-3 days, the beginning is slow, subfebrile temperature, cough is loud, hoarseness, laryngoscopy reveals swelling and hyperemia of the mucous membranes. The younger the child, the faster is the stenosis with aphonia and respiratory distress. Growing toxicosis, cyanosis, hypoxia is apparent. Laryngoscopy reveals grayish membranes along with hyperemia of the larynx and vocal cords. This stage lasts for 2-3 days. The sub-compensated phase is characterized by persistent stenosis, shortness of breath, stridor at rest, respiratory insufficiency. Decompensated stenosis is characterized by a sudden agitation, pulse wave loss on the inspiration is observed. The asphyxial stage lasts for several minutes, the breathing becomes superficial, overall cyanosis, isolated breaths, bradycardia, respiratory arrest is observed.

ASLT and diphtheritic croup should be **differentiated** from epiglottitis (edema and inflammation of the epiglottis), pneumonia, airway foreign bodies, allergic stenosis, laryngospasm in children with rachitis, spasmophilia. In this case, in addition to the anamnesis, dynamics of the disease, clinical and radiological studies, direct laryngoscopy and bronchoscopy are crucial.

The prognosis for ASLT and diphtheritic croup is serious with lethal outcomes in some cases, even if timely comprehensive treatment is provided.

The ASLT therapy is complex and dependent on the stage of the disease and its form. The treatment involves a pediatrician, otorhinolaryngologist, and resuscitation therapist. Children with stenotic laryngotracheitis should be hospitalized regardless of the clinical form and stage of the disease. During the first hours from the onset of the disease, warm drink, warm compresses around the neck, mustard plaster on the front surface of the neck and chest, warm socks, filled with irritants (e.g, dry mustard) is imperative. These activities have a beneficial effect on the course of the disease and may even stop it at the beginning. In addition, cool mist administration is recommended, similar to acute catarrhal [15-16].

In laryngeal stenosis of the first degree, cool mist administration using the state-of-the-art «Nebulizer» ultrasound devices to inhale «Ventolin» (salbutamol with ambroxolum), hormonal therapy: hydrocortisone dosed at 3-5 mg/

Table II. Differential diagnostic criteria for diseases with croup-like symptoms

Symptoms	Parainfluenza	Diphtheria	Chicken pox	Measles
Onset	Acute, less frequently sudden	Gradual, sequential change of periods	Acute	Acute
Hallmarks	Catarrh of upper respiratory tracts, laryngitis	Barking cough, shortness of breath, respiratory failure	Exanthema	Catarrh of upper respiratory tracts, conjunctivitis, rush
Appearance	Unmarked	Unmarked, skin paleness, cyanosis in 3rd degree stenosis	Polymophous skin rush	Swollen; hyperemia of face, conjunctivitis, exanthema from day 3-5
Catarrh manifestation	Prominent, coryza, cough	Absent	Absent	Prominent
Lethargy, adynamia	Mild	Prominent	Absent	Absent
Coryza	Moderate or prominent	Absent	Absent	Prominent
Cough	Dry, harsh	Barking, followed by soundless	Less common	Dry, productive
Voice	Hoarse	Hoarse, followed by aphonia	Without changes	Could be hoarse
Oropharyngeal lesions	Moderate hyperemia	No	No	Moderate hyperemia, enanthema
Lymphadenitis	No	Regional	No	Often multiple

kg body weight or prednisolone dosed at 1-2 mg/kg body weight for 2-4 days, which can be discontinued without reducing the dose, is advisable. Various decongestant mixtures in the form of aerosols, for example: 0.1 % solution of 1ml adrenaline hydrochloride; 1 % solution of 1ml dimedrol; 1 mg chymotrypsin in 1 ml; 1ml hydrocortisone (25 mg). 2 ml of the above mixture is administered for one inhalation 3 times a day. Other anti-inflammatory mixtures can be used. Antihistamines, multi-purpose drugs, sedative and vitamin therapy is recommended.

Laryngeal stenosis of the second degree requires the increase in the dosage of hydrocortisone from 5 to 10 mg/kg body weight, prednisolone up to 5 mg/kg for 5-7 days. The cool air in the ward is imperative for better activity of the ciliated epithelium. Currently, air humidifiers are widely used. Dehydration and detox therapy at a dose of 20 ml/kg, acritical mixtures to reduce the anxiety of the patient is advocated. Treatment should begin already on admission not to waste time. Prompt administration of spasmolytics to arrest swelling spread (2 %No-Spa® 1-2 mg/kg, papaverin 2 % 0.1-0.2 ml/year of life) is imperative. In croup growing 30 mg/kg mucolvane in 0.9 % sodium chlorideis administered jet intravenously. The use of diazolin is contraindicated, since it increases hyperproduction of the mucous membrane.

Laryngeal stenosis of the third degree requires even more intensive anti-inflammatory, dehydration, infusion and oxygen therapy. The dose of hormonal drugs should be increased, for example, hydrocortisone from 10 to 25 mg/kg, prednisolone up to 10 mg/kg; 2 % solution of euphyllin at a dose of 2-3 mg/kg. To reduce metabolic acidosis, 4% solution of sodium bicarbonate is administered at a dose of 4-5 mg/kg body weight intravenously. Symptomatic therapy is indicated. In the presence of hyperthermia, antipyretic drugs and cooling the child by applying cold to the projection of major vessels is recommended. In most cases, such intensive therapy gives a positive outcome within 2-4 hours. For agitated children intramuscular 0,5 ml aminazine or 1 ml droperidol are recommended for children from 6 months to 1 year of age; from 1 to 4 years of age intramuscular 1.0 ml aminazine or 2 ml droperidol; ½ tab of glycine sublingually 3 times a day can be used for older children. It should be remembered about biological role of calcium, which is the basis of bone tissue, stimulator of nerve impulses, universal regulator of muscle contraction, an important component of coagulation system. Hypocalcemic state is noted in the genesis of laryngospasm in the viral ASLT. Reduce in calcium concentration in blood plasma is associated with the severity of the condition in spasmodic forms. Therefore, it is rational to use medicines containing calcium (e.g., Calcium-D3 Nycomed) at a dose of 1250 mg during 1-2 intakes. The common treatment approach includes broad-spectrum antibiotics on indications. In case of viral etiology of the disease, oseltamivir is recommended in influenza, Novirin in ARVI (from 2 year of age), 50 mg/kg inosine pranobex up to 4 times a day from the first months of life, if necessary. In worsening of the overall health sate, tracheobronchial toilet is conducted by direct laryngoscopy, introducing proteolytic enzymes, hormonal medications, low concentration of antibiotics into the trachea with their subsequent suction together with pathological mass of the trachea and bronchi. In the dry form of ASLT with obstructive crusts, this gives very positive effects. In case of ineffectiveness of the above intensive therapy, intubation is performed using general anesthesia for 3-4 days in children under the age of 3 years, for 5-8 days in children of school age.

If the signs of edema are the forefront of clinical symptomatology, then the emphasis is placed on hormone therapy in age-related dosages as indicated above; in spasmodic form sedatives are beneficial; in hypersecretory form mucolytics are recommended. Table II presents differential diagnostic criteria for diseases with croup-like symptoms [11, 15].

If diphtheria was confirmed by the findings of differential diagnosis and laboratory studies then treatment is provided according to the protocol.

Treatment of diphtheria (according to the international protocols):

Basic therapy with antidiphtheritic serum (ADS) according to Bezredko (doses are in 1000 IU) according to international protocols.

In toxic and hypertoxic forms, 1 dose of ADS is administered intravenously drip-feed together with corticosteroids (30-50 mg single dose similar to prednisolone regimen). In combined forms, the amount of ADS is added. For children in the first two years of life, the dose of ADS is half reduced, compared with older children; for children under 8 years 2/3 of the dose is administered.

Intensification. Antibiotics: erythromycin, rulid, penicillin, cephalosporins, lincomycin, (age doses) for 7-10-14 days.

Supportive therapy: desensitizes, vitamins B, C or ascorutin, irrigation of the oropharynx with disinfectant solution.

Syndromic therapy: detoxification, (5 % glucose solution, 0.9 % sodium chloride solution) cumulative dose is 50-100 ml/kg/day; 5-10 mg/kg hydrocortisone or 1.5-2.5 mg/kg prednisolone in toxic forms, protease inhibitors (10-20.000 U contrycal, Gordox®), 150-500 U/kg heparin (in hemorrhagic syndrome).

Patients that are clinically healthy, with negative bacteriological test (twice within 3 days after the completion of antibiotic therapy, at an interval of 2 days) are ***discharged*** from the hospital on day 14-21 in mild and moderate forms and on day 30-60 in severe form. Surveillance by a pediatrician for 6 months is mandatory [17].

Treatment of carriers: vitamin therapy, antibiotics: 30-50 mg/kg/day erythromycin for 7 days. Ultraviolet irradiation of the tonsils, immune modulators is advocated.

Prevention. Non-specific (hospitalization and sanation of patients and carriers, quarantine at the focus of infection for 10 days (examination, swabs) and disinfection) and specific (DTaP vaccine from 2 months of age 3 times with the interval of 30 days (2, 4, 6 months) at a doseage of 0.5 ml i/m; DTaP revaccination at the age of 18 months, following with DT – anatoxin at 6, 16, 26 years old, then every 10 years [18-19].

We have made the analysis of the absolute and relative number of children vaccinated in 2006 and 2009 (vaccination and revaccination) among the population of Poltava region. The results of this comparison were disappointing. The findings of the comparison revealed the twice lower number of the vaccinated children in almost all positions. Apparently, such a significant decrease could not occur very rapidly or suddenly and it can be assumed that since 2007, a steady tendency towards the reduction of active immunization of children in Poltava region has been formed that was confirmed by the comparison of diphtheria vaccination in 2016 (only 28.4 %), which is by 3.2 times less than in 2006 [20].

We report a clinical case of the 8-year-old male patient V., with lethal outcome in 1993 (archival data from the Poltava Infectious Hospital). The boy was hospitalized in the intensive therapy and critical care unit at Poltava Infectious Hospital.

Complaints on hospitalization: sore throat, general weakness. The epidemic history revealed that the child was from a Gypsy family that partially migrated. The boy was not vaccinated. 7 days have passed since the onset of the disease. At the time of admission, the patient was in the moderate state of health and responded adequately to physical examination and questions. The skin was swarthy, slightly reduced in nutrition. Peripheral submandibular lymph nodes were dense, elastic and slightly painful on palpation, with the diameter of 0.7 cm. Mucous membrane of the pharynx was hyperemic, swollen with white patches, difficult to remove. Respiratory rate was 20 per minute, heart rate of 86 beats per minute. Auscultation of lungs reveals normal breath sounds. The borders of the heart were extended 1 cm to the left; heart auscultation revealed indistinct heart tones, tachycardia. The liver protruded 1.5 below the costal margin. Complete blood count revealed elevated ESR, leukocytosis, neutrophilosis; urinalysis revealed moderate erythrocyturia, leukocyturia, proteinuria. Bacteriological study of mucus from the throat revealed a toxigenic strain of *Corynebacterium diphtheriae*. Consultations that involved an ENT specialist, cardiologist, nephrologist was made. Biochemical and instrumental studies that include ECG, Phono CG, abdominal ultrasound, chest X-ray were conducted. Treatment was made according to the protocol, including administration of anti-diphtheria serum, antibiotic therapy, hormone therapy, detoxification therapy, cardiology therapy. On the third day of the patient's stay in the ICU, the health state dramatically worsened. On examination, the skin was pale, no patches in the throat were noted, and no swelling of the surrounding tissues was observed. Body temperature was 36.8 °C, the pulse was weak, 76 beats per minute, heart tones sharply weakened; ECG showed extrasystoles and splitting of the second heart tone. The liver protruded 3 cm below the costal margin. Coffee ground vomitus was observed. Consultation of leading experts was conducted and therapy was corrected. The child's condition continued to deteriorate and a lethal outcome was verified. There were no differences between clinical and postmortem diagnosis. According to the protocol of the postmortem consultation the diagnosis was made: pharyngeal diphtheria, toxic form. Toxic myocarditis. Necrotic colitis of 3-4 degree. Necrotic nephrosis. Bilateral lower lobe pneumonia. Pulmonary edema. Brain edema. Ascites. Hydrothorax.

CONCLUSIONS

Thus, pediatricians, family doctors, infectiologists should carry out prophylaxis among the population regarding the need for timely vaccination against diphtheria, as it is a reliable measure of preventing morbidity and reduction

the risk of complications and toxic forms, leading to lethal outcomes, especially among children [19-20].

REFERENCES

1. van Wijhe M., Tulen A.D., Altes H. et al. Quantifying the impact of mass vaccination programmes on notified cases in the Netherlands. Epidemiology & Infection. 2018;146(6):716–722. doi: 10.1017/S0950268818000481.
2. Lodeiro-Colatosti A., Reischl U., Holzmann T. Diphtheria outbreak in Amerindian communities, Wonken, Venezuela, 2016–2017. Emerg. Infect. Dis. 2018;24:1340–1344. doi: 10.3201/eid2407.171712.
3. Dureab F., Al-Sakkaf M., Ismail O. et al. Diphtheria outbreak in Yemen: the impact of conflict on a fragile health system. Confl. Health. 2019;13:19. doi: 10.1186/s13031-019-0204-2.
4. Murhekar M. Epidemiology of diphtheria in India, 1996–2016: implications for prevention and control. Am. J. Tropical Med. Hyg. 2017;97(2):313–318. doi: 10.4269/ajtmh.17-0047.
5. Finger F., Funk S., White K. et al. Real-time analysis of the diphtheria outbreak in forcibly displaced Myanmar nationals in Bangladesh. BMC Med. 2019;17(1):58. doi: 10.1186/s12916-019-1288-7.
6. Page K.R., Doocy S., Reyna Ganteaume F. et al. Venezuela's public health crisis: a regional emergency. Lancet. 2019;393(10177):1254–1260. doi: 10.1016/S0140-6736(19)30344-7.
7. Daniyarova A., Amireev C., Nazhmedenova A. et al. Analiz zabolevaemosti difteriej v respublike Kazakhstan [Analysis of the incidence of diphtheria in the republic of Kazakhstan]. Vestnik KazNMU. 2014;2(2):480–483. (In Russian).
8. World Health Organization. Diphtheria vaccine: WHO position paper, August 2017 - Recommendations. Vaccine. 2018;36(2):199–201. doi: 10.1016/j.vaccine.2017.08.024.
9. Hladka O., Sirenko I. Kharakteristika stanu shheplenosti` doroslogo naselennya Ukrayini, yake zakhvori`lo na difteri`yu u 2000–2010 rr [Characterization of vaccination status of adult population with diphtheria in Ukraine in 2000–2010]. Problemi vi`js`kovoyi okhoroni zdorov'ya. 2014;42(2):102-109. (In Ukrainian).
10. Ministry of Health of Ukraine reporting. https://life.pravda.com.ua/health/2019/10/29/238712.
11. Fedyak I.O., Bilyk I.P., Ivanuylyk I.I. Anali`z zakhvoryuvanosti` na vakczinokerovani` i`nfekczi`yi u ri`znikh kranakh svi`tu [Analysis of the incidence of vaccine controlled infection in different countries]. Zdobutki kli`ni`chnoyi i` eksperimental`noyi mediczini. 2015;1: 122–128. (In Ukrainian).
12. Wagner K.S., White J.M., Crowcroft N.S. et al. Diphtheria in the United Kingdom, 1986–2008: the increasing role of Corynebacterium ulcerans. Epidemiol. Infect. 2010;138(11):1519–1530. doi: 10.1017/S0950268810001895.
13. Reynolds G.E., Saunders H., Matson A. et al. Public health action following an outbreak of toxigenic cutaneous diphtheria in an Auckland refugee resettlement centre. Commun. Dis. Intell. Q. Rep. Commun Dis Intell Q Rep. 2016;40(4): 475–481.
14. Maximova N.M., Yakimova T.N., Markina S.S. et al. Difteriya v Rossii v 21 veke [Diphtheria in Russia in the 21st Century]. Epidemiologiya i vakczinoprofilaktika. 2017; 5(96):4–15. (In Russian).
15. Chernishova L.I. I`nfekczi`jni` khvorobi u di`tej: pi`druchnik (VNZ IV r. a.). Kiyiv: Mediczina. 2017: 569–582. (In Ukrainian).
16. Polyakova A.S., Bakradze M.D., Tatochenko V.K. Sindrom krupa u detej: predrassudki i dokazatel`naya mediczina [Croup syndrome in children: prejudices and evidence-based medicine]. Farmateka. 2018;1(354):15–22. (In Russian).
17. Krasiuk L.S., Chudna L.M., Svita V.M. et al. Aktual`ni` pitannya profi`laktichnikh zakhodi`v pri difteri`yi [Current issues of preventive measures in diphtheria]. Profilaktichna mediczina. 2015;1–2(24):76–80. (In Ukrainian).
18. Lovie-Toon Y.G., Hall K.K., Chang A.B. et al. Immunisation timeliness in a cohort of urban Aboriginal and Torres Strait Islander children. BMC Public Health. 2016;16(1):1159. doi: 10.1186/s12889-016-3825-z .
19. Ministry of Health of Ukraine reporting. https://moz.gov.ua/article/ministry-mandates/nakaz-moz-ukraini-vid-18052018--947-pro-vnesennja-zmin-do-kalendarja-profilaktichnih-scheplen-v-ukraini
20. Picul E.V., Il'chenko V.I., Il'chenko M.N. et al. Problemy aktyvnoyi imunizatsiyi u ditey Poltavskoyi oblasti [Problems of the active children immunization in Poltava region]. /World of medicine and biology. 2010;4:48–53. (In Ukrainian).

ORCID and contributionship:

Kateryna V. Pikul: 0000-0002-5724-4343 A,B,C,D,E,F
Lyudmyla M. Syzova: 0000-0002-8335-3295 A,B,C,D,E,F
Valentina I. Il'chenko: 0000-0002-1451-442X D,E,F
Irina M. Zvyagolska: 0000-0001-7531-3966 D,E,F

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Lyudmyla M. Syzova
Ukrainian Medical Stomatological Academy
23 Shevchenko st., 36024 Poltava, Ukraine
tel: +380662128133
e-mail: isizof@gmail.com

Received: 04.03.2020
Accepted: 15.10.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article