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СИНДРОМ КРУПА У ДЕТЕЙ

CROUP SYNDROME IN CHILDREN

Учебно-методическое пособие

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Изложены вопросы этиологии, патогенеза, клинической картины, диагностики, лечения синдрома крупа у детей.

Предназначено для студентов 4-го, 6-го курсов медицинского факультета иностранных учащихся.

ABBREVIATIONS

ARIs — acute respiratory infections
DAT — diphtheria anti-toxin
e. g. — exempli gratia (from Latin) that means for example
etc. — et cetera
ESR — erythrocyte sedimentation rate
FB — foreign body
FBA — foreign body aspiration
Hib — Haemophilus influenza type b
ICD — International Classification System of Diseases
i. e. — id est (from Latin) that is to say
ILO — inducible laryngeal obstruction
IM — intramuscularly
IV — intravenously
SARS-CoV-2 — severe acute respiratory syndrome — coronavirus 2
VCD — vocal cord dysfunction

GLOSSARY

Coryza — catarrhal inflammation of the mucous membrane in the nose.

Stridor — an abnormal, high-pitched sound (noise) produced by turbulent airflow through a partially obstructed airway at the level of the supraglottis, glottis, subglottis, or trachea. There are several types of stridor:

– inspiratory stridor results from laryngeal obstruction, the sound is heard during a prolonged inspiration;

– expiratory stridor results from bronchial obstruction, the sound is heard during a prolonged expiration;

– biphasic stridor is a combination of both inspiratory and expiratory respiratory sound and typically implies an obstruction in the midtracheal anatomy between the upper and lower airways.

The **steeple sign** — a radiologic sign most commonly found in patients with croup characterized by subglottic narrowing, giving the upper trachea a conical shape reminiscent of a church steeple or a wine bottle.

The **thumb sign** — a radiological feature in epiglottitis in which the epiglottic shadow appears thickened and rounded on a lateral soft-tissue radiograph of the neck.

Torticollis (i. e., wryneck) — a focal dystonia characterized by a state of excessive or inadequate muscle tone in the muscles in the neck that control the position of the head.

Trismus is the restriction of the range of motion of the jaws (difficulty opening the mouth), which typically stems from inflammation and spasm of masticator muscles.

MOTIVATIONAL CHARACTERISTICS OF TOPIC

Total in-class hours — 2.5.

Acute respiratory infections are the most frequent illnesses in childhood. The vast majority of ARIs have a viral aetiology. The viruses most frequently involved are adenoviruses, influenza viruses, parainfluenza viruses, respiratory syncytial viruses, and rhinoviruses. ARIs are more common in young children, have rather specific seasonal occurrences, and some agents are associated with specific respiratory syndromes including upper and lower airway obstruction that can be due to the development of croup or bronchial obstruction.

Croup is a common respiratory illness of the larynx and trachea that leads to inspiratory stridor, difficulty breathing, a barking cough, and can be life-threatening in some cases.

Historically, before the advent of treatment with corticosteroids and racemic epinephrine for severe croup, intubation, tracheotomy, and death were typical outcomes. Treatment has evolved from barbaric methods including bleeding and application of leeches, through mist kettles, mist rooms, to the current evidence-based practice of corticosteroids and nebulised epinephrine.

Despite the experience gained in the diagnosis and treatment of croup syndrome in children, there is still a risk of complications and rarely death. In this regard, relevant questions remain for diagnosis, management and prevention of infectious diseases accompanied by the development of croup.

The objective of the lesson. The purpose of teaching and learning consists in the formation of obtaining and getting to the student scientific knowledge about contemporary diagnosis and treatment of croup syndrome in children, taking into account the features of the clinical course of the disease, depending on the child's age and reactivity.

Class tasks. The students should *know*:

– aetiology, pathogenesis, clinical features of acute laryngotracheitis in children;

– indications for hospitalization of children with croup syndrome;

– specificity of laboratory diagnosis of diseases accompanied by croup syndrome and differential diagnosis with other conditions having similar manifestations;

– clinical symptoms and special characteristics of emergency conditions in children with croup.

The students should *be able to*:

– perform clinical examination of a child with croup syndrome, make the plan of examination, and identify the necessity of hospitalization;

– evaluate the results of examination of patients with croup syndrome, make a clinical diagnosis;

– fill in medical documents in cases of croup syndrome.

The students should *master*:

– methods of epidemiological analysis of development of croup syndrome in children;

– methods of identifying the clinical symptoms, atypical, severe and complicated forms of diseases accompanied by croup syndrome;

– contemporary methods of clinical, instrumental and laboratory examination, methods of inpatient and outpatient giving first medical aid in life-threatening conditions;

– methods of treatment and rehabilitation of recovering children with croup syndrome;

– methods and form of sanitary education of the population.

Requirements for the initial level of knowledge. Revise:

– Human Anatomy: anatomical and morphological structure of the respiratory system in children;

– Microbiology, Virology, Immunology: properties of the pathogens caused croup syndrome in children;

– Pathologic Physiology: patterns of occurrence and mechanisms of the development of pathological processes in the respiratory tract;

– Biological Chemistry: molecular basis of development of pathological processes, basic principles of biochemical diagnostic methods;

– Propedeutics of Internal Diseases: examination approaches, clinical and laboratory parameters evaluation;

– Pathologic Anatomy: general patterns and mechanisms of development of croup syndrome;

– Pharmacology: pharmacological properties of antibiotics, corticosteroids, antipyretics and the basis of their clinical application, directions for the use.

Questions for self-control from related disciplines:

1. Give a description and name the main properties of respiratory viruses and Corynebacterium diphtheriae.

2. Give the characteristic of specific anatomical and physiological features of the respiratory system in children that promote the development of croup.

3. Give a description of general patterns and mechanisms of development of croup syndrome.

4. What are the non-infectious causes of croup in children?

Test questions on the topic of the lesson:

1. Give a definition of croup syndrome in children. What is true croup? What is false croup?

2. What is the aetiology of croup diseases?

3. What is the pathogenesis mechanism of the development of croup in children?

4. What are the clinical manifestations of acute obstructive laryngotracheitis in children?

5. What are the clinical manifestations of laryngeal diphtheria in children?

6. Describe the degrees of laryngeal stenosis. Name the signs determined croup severity.

7. How to differentiate between diseases accompanied by development of croup syndrome?

8. Describe the management of patient with croup syndrome.

9. What emergency care should be provided to the patient with croup?

INTRODUCTION

Croup syndrome is a rapidly developing difficulty breathing in the airways due to narrowing of the airway lumen over a few seconds, minutes, hours, or days.

Croup links a group of diseases having similar symptoms (laryngitis, laryngotracheitis, laryngotracheobronchitis, etc.), but it does not a separate nosological entity or diagnosis.

Historically, two types of croup were distinguished: «true» croup (diphtheritic origin), and «false» croup (non-diphtheritic origin).

Nowadays, the term croup generally refers to an acute respiratory illness characterized by a distinctive barking cough, hoarsness, and inspiratory stridor in a young child, usually between six months and three years old, mostly caused by viral aetiology (*Parainfluenza virus*). In further describing, we will use the term croup to refer to its most common variant — an acute obstructive viral laryngotracheitis.

Classification of diseases related with croup syndrome in ICD-10 for Mortality and Morbidity Statistics includes:

A36.2 Laryngeal diphtheria

J05.0 Acute obstructive laryngotracheitis (croup)

J38.5 Laryngeal spasm (i. e., stridulus, spasmodic croup)

J38.7 Other diseases of larynx.

Most children develop croup only once or twice. Some children have recurrent episodes of croup, however, which is often referred to as «spasmodic croup.» Spasmodic croup also has been applied to cases that tend to be sudden in onset, often at night, with minimal coryza and fever, and that occur among children

with a family history of croup or atopy. It can be triggered by different reasons such as infection, gastro-oesophageal reflux, airway abnormality (e. g., tracheomalacia, subglottic narrowing), eosinophilic oesophagitis, airway hyperreactivity, and other still unknown factors. In some children, the case of relapse can be multifactorial.

Also, for describing patients who have greater than two or three episodes of croup the term «recurrent croup» is typically used. In children with recurrent croup, the frequency and severity of symptoms decrease with age and they usually subside between 6–12 years of age (as a result of airway diameter increase and maturation of the immune system).

In addition, the novel term «atypical croup» has been proposed in academic literature, defined as a child who presents with croup that is either:

a) severe, necessitating definitive airway management;

b) prolonged, symptoms persisting for 7 or more days despite medical therapy;

c) untimely, presenting at an age younger than 6 months or older than 6 years;

d) associated with an atypical pathogen, or

e) presenting with an airway lesion other than the classically described steeple sign on X-ray imaging.

Since the croup is an acute medical emergency, the primary physician must know how to provide emergency assistance to children with croup, when and where to send these children in order to prevent complications and fatalities.

HISTORICAL BACKGROUND

Francis Home (1719–1813), the Scottish military surgeon later a professor of the university, president of the Royal College of Physicians of Edinburgh, first described croup and diphtheria as a clinical entity. He introduced the novel word «croup» in his treatise (1765), «An Inquiry into the Nature, Causes and Cure of the Croup», in which he described 12 patients with croup. The term croup is descended from an Anglo-Saxon word kropan or the old Scottish term roup, which meant «to cry out in a shrill voice».

Fortunately, his unique essay had survived to this day. This is how he described his observations about croup: «It seems easy, in general, to distinguish the Croup from all other diseases hitherto described. A peculiar sharp shrill voice, not easily described; a remarkable freedom from all complaints, when in imminent danger, so that they will eat a minute before they expire; a quick laborious breathing; a frequent pulse, sometimes strong at first, but always soft and weak towards the end; scarce any difficulty of deglutition, or remarkable inflammation in the fauces; a dull pain, often, and sometimes an external swelling in the upper part of the trachea; senses quite distinct to the last; and all the symptoms most rapid in their

progress, characterise sufficiently this disease. I have not mentioned a cough, as that symptom is sometimes absent; and when it attends the Croup, it is not of the common kind, but more short and stiffled, and less convulsive, with little or no expectoration».

Pierre-Fidèle Bretonneau (1778–1862), a physician of Tours, who became world-famous thanks to the identification of specific features of diphtheria, first completed a successful tracheotomy in a child with diphtheritic croup, and advanced the doctrine of specificity of disease before the general acknowledgement of the germ theory of infectious maladies. During the epidimic of malignant sore throat in Tours (1818–1820) he carried out his clinical-pathological studies of malignant croup of precisely children who died of shortness of breath, and he came up with the name «diphtheria» (derived from the Greek. diphthera = membrane). He proposed the name *diphtheritis* (diphtherias); however, the term was changed later to diphtheria (diphthérie).

The characteristic cough and stridor have also been described by Ley Hugh Churchill (1790–1837) as «the crowing of a cock, the yelping of a fox, the barking of a dog, the braying of an ass, or a ringing sound, as if the voice came from a brazen tube» in his essay on the laryngismus stidulus, or croup-like inspiration of infants in 1836.

For the 19th century, the term croup was applied to numerous probably viral and bacterial diseases, which included diphtheria and «cynache trachealis», which was often called «membranous» or «true» croup, as opposed to «spasmodic» or «false» croup. In 1883, Edwin Klebs (1834–1913) demonstrated that *Corynebacterium diphtheriae* was the agent of diphtheria. In 1948, Edward F. Rabe (1918–1998) classified the forms of infectious croup according to aetiology — bacterial or nonbacterial — and suggested that the latter, larger group was viral in origin.

AETIOLOGY AND EPIDEMIOLOGY

Parainfluenza viruses, types 1, 2, and 3 are the most frequent cause of croup, accounting for more than 60 per cent of cases. Less frequently associated with croup are influenza A and B, respiratory syncytial virus, adenovirus, rhinoviruses, human coronavirus NL63, human metapneumovirus, coxsackieviruses, echoviruses, and measles. Immunosuppressed patients may have croup caused by herpes simplex virus or fungi. The origin of croup in children is very diverse and continues to be replenished with new aetiological agents. Thus, a few cases of paediatric SARS-CoV-2 croup were described recently.

Bacterial laryngotracheitis and laryngotracheobronchtitis often present as a secondary illness following an acute respiratory viral infection. Viral co-infection particularly with parainfluenza type 1 and influenza virus is typical. Among

bacterial agents the most common are: *Streptococcus pneumoniae*, *Haemophilus influenza*, *Streptococcus pyogenes*, and *Staphylococcus aureus*. Also, croup may be caused by atypical agents, such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* alone or in combination with respiratory viruses.

Croup occurs most commonly between the ages of 1 and 6 years, with a peak incidence being around 18 months of age and the majority of cases below 3 years of age. It is more common in boys than girls.

In temperate climates, parainfluenza croup is most common during the late fall and winter, although cases can occur throughout the year. The mechanism of transmission is airborn via droplets, that are spreading by talking, coughing, and sneezing. The source of infection are only humans.

All cases of obstructive laryngotracheitis are communicable diseases with the highest index of contagiousness in viral infections.

PATHOGENESIS

The laryngeal anatomy of children makes them particularly susceptible to narrowing of the upper airways. The narrowest segment of the paediatric airway is the subglottic region, which is encircled by the rigid cricoid cartilage ring. Furthermore, this segment in children is significantly narrower than in adults. There is non-fibrous, loosely attached mucosa in this region that is well vascularized, is furnished with numerous mucous secreting glands, and easily obstructed in the presence of subglottic oedema. In addition, the cartilaginous support of the infant airway is soft and compliant, that enhances the airway collapse during inspiration.

The narrowing of the airway lumen of the larynx and trachea in croup occurs due to oedema and infiltration of the mucous membrane of the larynx and trachea, dynamic collapse, active constriction of the muscles of the upper trachea and larynx in the result of inflammation, and hypersecretion of the mucous glands of the larynx, trachea and bronchi.

Even minimal inflammation of the membranes lining the narrow passages of the larynx and glottis in a young child results in an appreciable degree of obstruction because resistance to airflow is inversely related to the fourth power of the radius of the airway. Nasal obstruction and crying can aggravate the dynamic narrowing of the child's airway further.

With the subglottic obstruction, the child's tidal volume initially declines. This is compensated by an increase in the respiratory rate to maintain adequate alveolar ventilation. If the degree of obstruction worsens, the work of breathing may increase such that the child tires and can no longer maintain an adequate respiratory effort. The tidal volume may decrease further, and, as the respiratory rate declines, hypercarbia and secondary hypoxemia ensue.

CLINICAL MANIFESTATIONS

The clinical presentation of croup are characterized by the following signs (in varying combination):
– hoarseness;
– «seal-like» barking cough;
– inspiratory stridor;
– difficulty breathing;
– respiratory distress.

Croup may be accompanied by a fever, coryza, other catarrhal symptoms, and rarely bronchial obstruction.

There can be two scenarios for the development of viral croup: with a gradual onset and preceding respiratory symptoms or an abrupt onset more often at night without prior complaints. For bacterial croup is only possible the gradual onset.

Acute laryngotracheitis generally starts with several days of rhinorrhea, pharyngitis, low-grade fever and a mild cough. Over the next 12 to 48 hours, a progressively worsening barking cough, hoarseness and inspiratory stridor are noted. The speed of progression and degree of airway obstruction can vary widely. In the majority of cases, the croup is mild or moderate. The onset of airway obstruction is often rapid and typically at night, in the early, predawn hours (e. g., from 00 : 00 to 3 : 00 am). Why croup symptoms tend to worsen at night is unknown, but a physiologically plausible explanation might lie with the known circadian fluctuations in endogenous serum cortisol, concentrations of which peak at about 08 : 00 am and reach a trough between 11 : 00 pm and 04 : 00 am. Croup symptoms appear to subside during the day only to recur the following night. Thus, a child with significant stridor presenting during daylight, may be more seriously affected. Symptoms of croup usually normalize over next 2–7 days.

Varied aetiological agents can contribute their own features to the clinical presentation of croup in children. So in obstructive adenovirus laryngotracheitis the cough is often productive, and the course of the disease is undulating. Croup resulting from influenza A is less common but more severe than croup arising from parainfluenza or respiratory syncytial virus.

SEVERITY ASSESSMENT

The crucial point is a proper determination of croup severity that defines further appropriate treatment. A lot of croup scoring systems have been proposed, but the Westley croup score has been the most widely used, which allows to give a unified objective assessment of clinical signs and helps in the next monitoring. The Westley croup severity score is presented in appendix 1. Severity is determined by

the mental status, the presence or absence of stridor at rest, pallor or cyanosis, air entry, and the degree of chest wall retractions.

There are four levels of croup severety: mild, moderate, severe, and impending respiratory failure.

Mild croup (Westley croup score of ≤ 2) — children have a barking cough, hoarse voice, stridor when crying, no stridor at rest, either no, or only mild, chest wall retractions.

Moderate croup (Westley croup score of 3 to 7) — children have pallor of the skin, cyanosis of the nasolabial triangle, a frequent barking cough, stridor at rest, mild to moderate chest wall retractions, when crying, but no or little distress or agitation.

Severe croup (Westley croup score of 8 to 11) — children have a frequent barking cough, stridor and marked retractions at rest (including indrawing of the sternum), persistent cyanosis of the lips, significant distress and agitation.

Impending respiratory failure (Westley croup score of ≥ 12) — children have depressed level of consciousness, marked pallor or extended cyanosis, decreased or absent breath sound, stridor and severe retractions at rest, poor air entry.

With the onset of complete obstruction, stridor may become barely audible as minimal air moves through the critically narrowed airway.

DIAGNOSIS

History and physical examination are crucial for a diagnosis of croup. The diagnosis is usually established on the basis of clinical symptoms. In a typical course of disease, no further laboratory tests are necessary. When X-ray imaging is conducted the anteroposterior view classically shows a «steeple sign» in the subglottic area. But the classic radiographic findings may be absent in 50 per cent of patients and are also not pathognomic for croup.

Recurrent episodes, atypical course of disease, rising suspicion of predisposing causes (i. e., a narrowing of the larynx or trachea), a gastro-oesophageal reflux are situations that indicate a need for an endoscopic examination.

Characteristic abnormalities in a blood test can help to interpret the aetiology of the disease (viral or bacterial). However, it should be remembered that, the blood test in children with marked clinical signs of laryngeal stenosis, performed particularly on the first day of a viral disease, often reveals a high level of white blood cells and neutrophilia, which do not suggest a bacterial infection in these cases.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for croup is broad and it is important to consider uncommon causes, particularly in severe cases or cases with unusual course.

Foreign body aspiration is a potentially life-threatening emergency that most commonly occurs in children younger than 3 years. In the majority of cases food items (nuts, seeds, raisins, ect.) or other radiolucent substances are aspirated. A foreign body can become stuck in either the upper or lower airway. Predominantly the FB is lodged in the main and intermediate bronchi. The minority of FB get stuck in the larynx and trachea that leads to partial or complete laryngeal obstruction and the development of clinical pattern of croup.

The presentation of a laryngeal FB depends upon the size, shape, site, nature of FB, and the degree of obstruction leading to a great variability in symptoms. The presence of a lumen within the FB permitting ventilation and the inert nature of the FB are factors responsible for relative lack of symptoms. The symptomatology of laryngeal FBs depends on whether it produces complete or incomplete airway obstruction. In complete airway obstruction, the presentation is with catastrophic respiratory distress leading to apnea, cyanosis, loss of consciousness, and sudden death if FB is not dislodged. However, incomplete laryngeal obstruction may present with less severe non-specific symptoms such as dysphonia including hoarseness, a barking cough, difficulty breathing and possible misdiagnosis or delay in diagnosis. Laryngeal FBs may also manifest with symptoms related to the oesophagus, such as dysphagia, gagging, or throat discomfort.

A FBA classically presents in three phases. The first phase is impaction of the FB, resulting in acute coughing, choking, stridor, respiratory distress and potentially cyanosis. Choking lasts for a few seconds to several minutes after the episode and may be self-limited. Patients then commonly progress to an asymptomatic phase, which accompanied by reduction in the respiratory tract reflexes over time. The third phase involves manifestations such as dysphonia, chronic cough, and secondary infections.

FBA in children should be suspected on the basis of a sudden-onset coughing and choking episode if such an episode is witnessed by an adult or remembered by the child. The absence of coryza, sore throat and cough in a paediatric patient with acute onset respiratory symptoms should raise doubts of an infectious aetiology. Also it is needed to exclude other reasons of croup includig a FBA in cases poorly responding to medical line of management. Flexible endoscopy of the airway should be performed if the history and physical examination are suggestive of an aspirated FB and should not preclude a decision for direct laryngoscopy and rigid bronchoscopy under general anesthesia for definitive airway survey in selected cases where diagnosis remains in doubt.

To prevent delays in diagnosis and subsequent complications, it is important that a high level of clinical suspicion is maintained when patients present with a vague history or symptoms that may represent FBA.

Epiglottitis (i. e., supraglottitis) is inflammation of the epiglottis and adjacent supraglottic structures. Inflammation results in airway oedema and lumen narrowing, which rapidly lead to life-threatening acute airway obstruction or even death without providing emergency assistance. Currently, acute epiglottitis is a rare disease that causes a severe clinical course and requires immediate admission to a hospital.

Epiglottitis is most frequently caused by infection. *Haemophilus influenza* type b used to be by far the most common cause of epiglottitis among children, accounting for 75–90 per cent of cases. The incidence of Hib-induced epiglottitis in children has declined since the introduction of vaccinations in countries where such vaccinations are routinely administered. However, severe Hib infections occur in children, sometimes even children who have been fully vaccinated. In areas of the world where Hib vaccination is not widespread, Hib remains a leading cause of meningitis and epiglottitis in children and pneumonia in adults.

Less common infectious aetiologies include Streptococcus pneumoniae, group A streptococci, Staphylococcus aureus, nontypeable H. influenzae, Klebsiella pneumoniae, Moraxella cattarhalis, Pasteurella multocida. It is noticed that the disease proceeds in this cases, as a rule, in a milder form.

Viruses have been implicated (e. g., parainfluenza virus, herpes simplex virus, Epstein-Barr virus, herpes zoster virus) and can encourage a superimposed bacteria to invade and cause epiglottitis. Recently several cases of epiglottitis have been described in adult patients with SARS-CoV-2. Candida and Aspergillus might be the cause of epiglottitis in immunocompromised patients.

Non-infectious causes of epiglottitis are much less common. Aetiologies include thermal causes (following scalds to face, neck and thorax which can occur even in absence of ingestion and intra-oral damage, as well as throat burns affecting the epiglottis of bottle-fed infants), caustic insults (e. g., automatic dishwasher soap ingestion), and direct trauma (e. g., blind sweep to remove FB).

Infectious epiglottitis results from bacteremia and/or direct invasion of the epithelial layer by the pathogenic organism. The primary source of pathogens is the posterior nasopharynx. Inflammation starts on the lingual surface of the epiglottis, before rapidly spreading to other laryngeal structures including the aryepiglottic folds, the arytenoids and supraglottic larynx. The lingual surface of the epiglottis and periepiglottic tissues have abundant networks of lymphatic and blood vessels that facilitate spread of infection and the subsequent inflammatory response.

The vast majority of paediatric patients with epiglottitis are children aged 1 to 5 years. It can occur throughout the year, but is more common in cold months. Clue and characteristic features of epiglottitis are acute onset of disease and rapidly

progressive respiratory failure accompanied by a high-grade fever, marked signs of toxicosis (e. g., restlessness, irritability, loss of appetite), dysphagia, drooling, and change of voice.

The first sign is usually a fever which can reach 40 degrees C (104 degrees F). Airway obstruction develops over several hours from the disease onset and progresses steadily. The appearance time of difficulty breathing depends upon aetiology and the child's age. The younger he is, the sooner signs of asphyxia will develop. If the child can share his complaints, he will tell about his severe throat pain. Therefore, refusal to eat and drink is caused not only by toxicosis. Cough is not an obligatory sign of epiglottitis, but it might present in some cases. The cough does not harsh and barking, and more often it is only a semicough; the voice is not hoarse, but muffled in contrast to presentation of viral croup. The child with epiglottitis might prefer to adopt a position of sitting up, leaning forward, with their chin pushed forward and they might refuse to lie down.

We reviewed the clinical histories of 30 children admitted to a clinical site of our department (City Children's Infectious Clinical Hospital) with epiglottitis (2002–2010). The diagnosis was confirmed by direct visualization of the epiglottis in all patients and isolation of Hib in blood cultures and/ or surface culture of the epiglottis in 22 cases (the definite aetiology was not established in 8 children with epiglottitis). Since 2011 cases of epiglottitis in our hospital have almost not been registered.

The greater majority of patients with Hib epiglottitis (86 %) were aged 1 to 5 years, males predominated (59 %). The disease started abruptly, children were mainly admitted to the hospital on the first day of illness onset (77 %). All patients had a serious condition due to respiratory failure and toxicosis. Corticosteroids were prescribed 63 per cent of patients in the prehospital stage and in the admission department (prednisone in a dose of 1–5.5 mg/kg or dexamethasone in a dose of 0.3–0.6 mg/kg IM). There was no clinical improvement in 100 percent of cases, which required endotracheal intubation. Respiratory distress, inspiratory stridor, and fever were the most common clinical manifestations (fig.). More than 95 per cent of children had leucocytosis upon admission $> 15 \times 10^9/L$ with neutrophilia $> 10 \times 10^9/L$, among them 73 per cent had leucocytosis $> 20 \times 10^9/L$, 32 per cent — neutrophil left shift, 46 per cent — increased level of ESR > 20 mm/h.

The most important thing is to distinguish rarely occurring acute epiglottitis from a common acute obstructive laryngotracheitis. We highlight that children with epiglottitis do not have a classic croupy cough, they often be drooling, appear more toxic, have higher fevers and rougher clinical course in contrast to viral croup. Where no clinical improvement is seen after the corticosteroid administration, epiglottitis should be excluded.
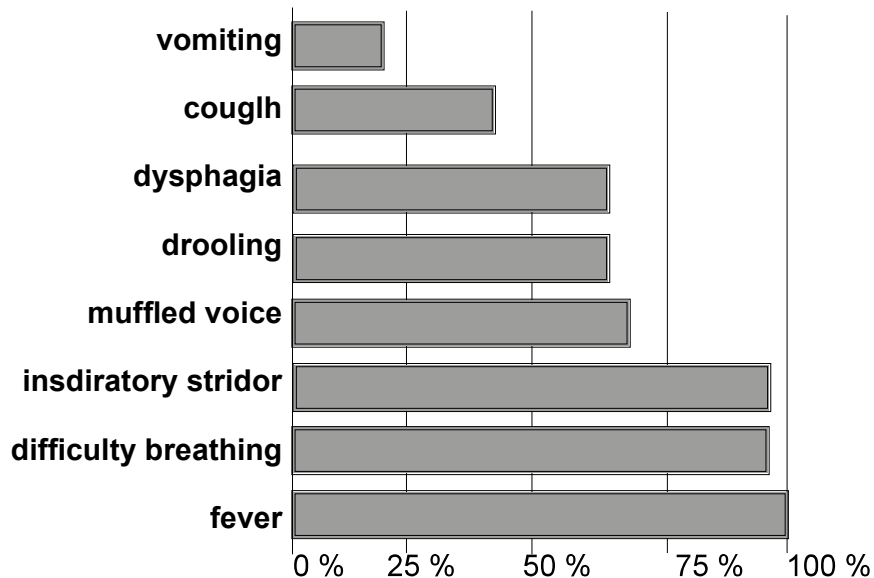
Fig. The clinical manifestations of Hib-epiglottitis in children upon admission to City Children's Infectious Clinical Hospital

The diagnosis of epiglottitis is usually made on clinical grounds. An oropharyngeal exam is not recommended because manipulation of the oral cavity might lead to respiratory arrest in case of epiglottitis. During direct visualization inflamed epiglottis appears cherry red, oedematous, and thickened. In some cases epiglottitis can be accompanied by uvulitis (a red swollen uvula).

A lateral radiograph of the neck can be used to find thickening of the epiglottis and aryepiglottic folds referred to as the «thumb sign». It is not necessary to make the diagnosis but can be used to narrow down the provider's differential diagnosis. This should only be performed in the most stable, comfortable, and cooperative of patients. Computer tomography is only rarely obtained, and usually when the diagnosis is unclear. Indeed, placing the child in the supine position can actually precipitate respiratory arrest. A flexible fiberoptic laryngoscopy can be performed theoretically, but only in a very controlled setting such as the operating room due to the risk of inducing laryngospasm. This is almost always never done.

If clinical suspicion for acute epiglottitis exists, the patient should be taken emergently to the operating room for airway examination under the most optimal conditions possible.

Laryngeal diphtheria is a life-threatening form of diphtheria, more typical for young children. The disease is generally occurs in individuals with a low antitoxic immunity and in unvaccinated people. The incidence of diphtheria has dropped dramatically since widespread implementation of vaccination. However, diphtheria is remained endemic in some regions in the world. And nowadays, diphtheria is a disease which many physicians no longer see in personal experience.

Diphtheria is caused by toxicogenic strains of *Corynebacterium diphtheriae*. It mostly spreads via airborne droplets. The incubation period is 2–10 days.

Laryngeal diphtheria can be primary or can occur from secondary extension from the oropharynx. The airway becomes blocked due to oedema, reflex constriction of the laryngeal muscles, and pseudomembrane formation in the larynx, trachea, and even in the lower respiratory tract.

Laryngeal diphtheria is characterised by a gradual onset over 2–3 days, low-grade fever, hoarseness, and in some cases development of aphonia. A barking croupy cough, similar to viral croup, and stridulous breathing (on inspiration, or biphasic occuring in the later stage) progressively increasing over next hours and days. The disease can lead to complete airway obstruction and asphyxia without appropriate treatment. In infants it can take only 1–1.5 days. When laryngeal diphtheria is concomitant with tonsillar diphtheria dysphagia presents and the characteristic membranous pharyngitis is seen on physical examination.

Angioedema (i. e., angioneurotic oedema) can present at any age and with rapid onset of dysphagia and stridor and possible cutaneous allergic signs such as urticarial rash. Children might have a history of allergy or previous attack. Angioedema typically affects areas with loose connective tissue, such as the face, lips, mouth, and throat, larynx, uvula, extremities, and genitalia. The clinical manifestations of laryngeal angioedema are similar to viral croup, which include: hoarseness, a barking cough, inspiratory stridor, however, without fevers and respiratory signs. Angioedema is diagnosed clinically.

Angioneurotic oedema can be classified into two main categories, such as allergic and non-allergic angioneurotic oedema. Non-allergic angioneurotic oedema can be subclassified into hereditary (i. e., C1-esterase-inhibitor deficiency), acquired, drug-induced and idiopathic.

The majority of angioneurotic oedema cases (about 90 %) are due to an allergic reaction that produces angioedema within minutes via eliciting a Type 1 hypersensitivity reaction (histaminergic mediated mast cells and basophil activation). In contrast, non-allergic angioneurotic oedema by inhibiting bradykinin may not be seen for months. Bradykinin is a potent vasodilatory mediator. Lack of C1-inhibitor activates the contact system (kallikrein-kinin), which finally leads to the overproduction of bradykinin, development of swelling of the mucosa and submucosal swelling.

Angiotensinogen converting enzymes inhibitors, angiotensin-2 antagonists, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, oral contraceptive pills, proton pump inhibitors and vaccines are common causes of drug-induced angioedema. Acquired angioedema can be caused by serious and/or chronic illnesses such as lymphoproliferative disorders, autoimmune disease, neoplastic conditions, and infections. Angioedema can be precipitated by any type of surgery, viral infection, exposure to heat and cold, pregnancy, minor trauma (e. g., dental work, tongue piercing), mental stress, and ingestion of certain foods.

Laryngeal oedema can be one of the respiratory manifestations of beginning life-threatening anaphylaxis along with cardiovascular, cutaneous, or gastrointestinal symptoms.

Inducible laryngeal obstruction. In clinical practice, physicians and paediatricians may encounter paediatric and adult patients with unexplainable episodes of stridor and difficulty breathing that are non-infectious or non-organic in origin. These disorders have previously been described as vocal cord dysfunction (synonyms: «paradoxical vocal-fold motion», «functional stridor», «Munchausen's stridor»). The average age at diagnosis of VCD was 14 years and almost 80 per cent of patients were females. However, it has to be mentioned that VCD has been reported even in infancy.

Currently, a novel term: inducible laryngeal obstruction has been introduced to describe these conditions. ILO is an inappropriate, transient, reversible narrowing of the larynx in response to external triggers. The most common inducers of laryngeal obstruction are exercise, emotional stress, and irritants which include gastrolaryngeal reflux, odours, cold air, environmental and occupational exposures, wood dust and chemicals. However, despite the growing understanding of these disorders, the prevalence and incidence in the paediatric population remains unknown.

The causal mechanism of irritant ILO is unknown. It is unclear if irritant ILO is a direct response to the irritant stimulus itself, e. g. via mucosal inflammatory reactions, or related to altered reflex sensitivity, and to what extent psychological factors contribute; highlighting the lack of evidence in the field.

The degree of laryngeal obstruction can vary from mild to severe, with near-complete closure in some cases. Typical clinical features are wheeze, dyspnoea and cough, and these symptoms are highly variable and evanescent. In most cases, individuals with ILO will exhibit inspiratory breathing difficulties, although a pure expiratory form of ILO has been described. Dyspnoea caused by exercise-induced laryngeal obstruction can be accompanied by coarse or high-pitched inspiratory breath sounds, sometimes progressing to clear-cut stridor, and may be associated with severe respiratory distress, hyperpnoea and/or panic reactions, evolving in parallel with increasing ventilatory requirements throughout the exercise session. Exercise-induced laryngeal obstruction can occur within a minute or less of intense exercise, and symptoms often resolve within 2 to 5 minutes of stopping the activity.

Considering the similar clinical picture of obstructive laryngotracheitis and ILO, in all cases of recurrent croup or in treatment failure, ILO should be suspected.

It is important to be aware of other possible reasons of croup. Another rare non-infectious cause of croup in children is **nephrotic syndrome**, which can be primary or due to relapse and is generally observed in older children. Laryngeal obstruction develops gradually over a week, and usually accompanied by other typical signs of nephrotic syndrome: oedema in the lower extremities, periorbital regions, face, and abdomen; anuria; urine changes. The intensity of stenosis can vary from mild to severe.

Electrolyte abnormalities such as **hypocalcaemia** can be a rare cause of stridor and laryngospasm. Infants with vitamin D deficiency and rickets, or children suffering from primary or acquired hypoparathyroidism may present acute upper airway obstruction due to severe hypocalcaemia.

Most infants with hypocalcaemia are asymptomatic, but those with symptoms demonstrate increased neuromuscular irritability, also known as tetany. This typically manifests as muscle jerking or twitching and, less commonly, can present as stridor due to laryngospasm. One should consider hypocalcaemia when evaluating a patient with unexplained stridor and/or apnoea and obtain a calcium level in addition to conventional modalities of airway evaluation.

Inflammatory diseases of the pharynx and the retropharyngeal space, such as peritonsillar and retropharyngeal abscess, can lead to the development of upper airway obstruction. **Peritonsillar abscess** is a common complication, often due to improper treatment of prior oropharyngeal infection, mostly occurred in school-aged children, adolescents, and young adults. Patients complain of a high-grade fever, malaise, progressively worsening throat pain, dysphagia. The physical examination reveals marked tender and painful submandibular and anterior cervical lymphadenitis, a muffled voice, trismus, erythematous, swollen soft palate with uvula deviation to contralateral side, and enlarged tonsil with or without exudates.

In contrast to peritonsillar abscess, **retropharyngeal abscess** is an uncommon but potentially life-threatening diagnosis. Retropharyngeal abscess occurs most commonly in children between the ages of two and four, as the retropharyngeal nodes involute after 5 years of age, infection in older children and adults is much less prevalent. Clinical presentation of retropharyngeal abscess is characterized by non-specific and highly variable signs including high-grade fever, irritability, toxic appearance of a child, throat and neck pain, neck stiffness, torticollis, refusal to eat and move the neck. Other signs can include a muffled voice, drooling, stridor, and respiratory distress in some cases. Clinical features may be reminiscent of epiglottitis. Physical examination can reveal bulging of the posterior pharyngeal wall, although this is present in less than 50 per cent of children. Cervical lymphadenopathy may also be present.

Diagnostic imaging is required in making diagnosis. A computed tomography scan of the neck with contrast is now the preferred imaging technique. A magnetic resonance imaging with gadolinium enhancement can demonstrate the presence and size of a retropharyngeal abscess, but this modality takes longer to obtain than does computed tomography scanning. Ultrasonography can be useful in the point of care.

In addition, the rare non-infectious causes of croup syndrome in children involve: **laryngeal trauma**, **thermal** or **chemical injuries**, **laryngeal papillomatosis**, and **neoplasms**.

The summary of differential diagnosis of croup in children is shown in appendix 2.

MANAGEMENT AND TREATMENT

Mild croup. Most children with croup have mild severity of the illness which can be treated at home. Management and treatment are supportive and symptomatic. Families should be instructed in supportive care and indications to seek medical attention.

Children with croup should be made as comfortable as possible, avoid agitating the child with unnecessary procedures because agitation and crying cause substantial worsening of symptoms. Children are recommended a plenty of oral fluids; antipyretics (acetaminophen or ibuprofen) to control fever (when axillary temperature $\geq$ 38.5 degrees C); exposure to cold night air; nebulized saline (sodium chloride 0.9% inhalation solution) or ambroxol hydrochloride (solution for inhalation) in order to improve mucus rheological properties.

Some authorities recommend treating children with mild croup with a single dose of corticosteroids (dexamethasone 0.15–0.6 mg/kg or prednisolone 1.0 mg/kg given orally), but we suggest that corticosteroids are warranted in children with moderate croup and at least is not to be needed in barking cough with no other symptoms.

Indications for inpatient admission include the following:
– moderate/ severe croup;
– impending respiratory failure;
– toxic appearance or clinical picture suggesting serious secondary bacterial infection;
– need for supplement oxygen;
– severe dehydration;
– young age, particulary younger than six months;
– recurrent visits to the emergency department within 24 hours.

Moderate to severe croup. The patients with clinical signs of moderate or severe croup should be admitted to a hospital (the other indications for hospitalization see above). Admission to the paediatric intensive care unit is warranted if any of the following are present:
– respiratory failure requiring endotracheal intubation;
– persistent severe symptoms requiring frequent nebulized epinephrine dosing;
– underlying conditions placing the child at high risk for progressive respiratory failure (e. g., neuromuscular disorders or bronchopulmonary dysplasia).

Families should be instructed in making the child as comfortable as possible, which is usually achieved by having the child sit in the lap of one of the parents/ caretakers, avoid agitation the child with unnecessary procedures. Simptomatic treatment is also be recommended, including fluid intake, antipyretics, inhalation with saline or mucoactive agent (see above).

Administration of corticosteroids is essentially important in all children with moderate to severe croup. Dexamethasone should be administered in a single dose of 0.6 mg/kg (maximum of 16 mg) by one of the possible route: oral, IM or IV. If oral intake is not tolerated and IV access has not been established, IM route should be used. The kinetics of oral dosing show a rapid peak in serum levels occurring within 1 hour.

After administration of dexamethasone nebulized epinephrine (racemic epinephrine or L-epinephrine) should be applied in all children with moderate to severe croup:

– racemic epinephrine is administered as 0.05 mL/kg per dose (maximum of 0.5 mL) of a 2.25% solution diluted to 3 ml total volume with normal saline via nebulizer over 15 minutes;

– L-epinephrine is administered as 0.5 mL/kg per dose (maximum of 5 mL) of a 0.1% (1:1000) preservative-free solution via nebulizer over 15 minutes.

One clinical trial found that L-epinephrine (5.0 mL, 0.1%) was as effective and safe as racemic epinephrine (0.5 mL, 2.25%). Nebulized epinephrine has an onset of effect within 10 minutes and waning of effect between 1 and 2 hours.

The child with moderate to severe croup should be continuously observed. Croup symptoms usually improve within 30 minutes after pharmacologic intervention. If there is no clinical improvement in croup symptoms in 1—2 hours, nebulized epinephrine should be repeated. If clinical response absents after repeated inhalation with epinephrine, consider alternative diagnoses. Nebulized epinephrine can be repeated every 15 to 20 minutes. However, children requiring frequent doses of epinephrine (more frequently than every 1 to 2 hours) are needed cardiopulmonary monitoring.

Additional respiratory support may be required for children with severe croup. Supplemental oxygen administration should be recommendered to the children having hypoxaemia (oxygen saturation of $\leq$ 92% in room air).

The need for intubation should be considered in children with progressive respiratory failure, paradoxical pulse, violation of the respiratory rhythm, marked excitation or depression of consciousness. Only 1—3 per sent of admitted patients with croup require intubation.

The majority of children with moderate croup have clinical improvement after initial treatment and can be discharged to home after 3 to 4 hours odservation (depending upon a country: e. g., at least after 24 hours of odservation in our country). Discharge criteria include the following: no stridor at rest, normal pulse oximetry, good air exchange, normal color, tolerating fluids by mouth, and caregivers understand instructions and are able to return for care if needed.

Epiglottitis. In cases suspected to epiglottitis a patient should be emergency transported to the intensive care unit. Effective airway management is critical. The first step is to oxigenate patient using bag-valve-mack ventilation with

100% oxygen during transportation in a sitting position. If the patient unstable or ventilation does not maintain oxygenation, the patient should be urgently intubated by direct laryngoscopy or bronchoscopy in a controlled setting (i. e., operating room or intensive care unit).

After airway management is complete, empiric antimicrobial therapy should be administred. The third-generation cephalosporins are first-line agents for infectious epiglottitis. Ceftriaxone is the antibiotic of choice. In patients with history of severe hypersensitivity to penicillin or cephalosporin antibiotics, vancomycin plus carbapenem antibiotic should be administered. Recommended antimicrobial treatment for infectious epiglottitis is indicated in appendix 3. The duration of antibiotic therapy ranges from 7–14 days (usually 10 days) depending on clinical improvement.

Laryngeal diphtheria. Despite a rare occurrence we highlight the need for keeping a high index of clinical suspicion and initiation treatment of diphtheria without delay. All patients with possible laryngeal diphtheria are required hospitalization with droplet isolation. The crucial point is airway management allowing access for mechanical removal of tracheobronchial membranes and preventing the risk of sudden asphyxia through aspiration. If there is suspicion for loss of the airway or respiratory failure, the endotracheal intubation should be considered.

Diphtheria anti-toxin should be given without waiting for laboratory confirmation. Early treatment with DAT is critical to neutralise circulating free toxin before it can irreversibly bind to tissues causing organ damage. The effectiveness therefore declines with time since onset of symptoms. Dosage for DAT is determined by the severity and duration of the disease, and the dose is the same for adults and children. According to the UK clinical guidance on diphtheria anti-toxin (issued May 2022), the recommended dosage of DAT for laryngeal or pharyngeal disease of less than 48 hours is 70,000 IU; for laryngeal or pharyngeal diphtheria of more than 48 hours, or severe disease (e. g., accompanied by extensive membrane or oedema («bull neck»)) is 100,000 IU. The IV route is the preferred route of administration of DAT, especially in severe cases. Tests to exclude hypersensitivity to horse serum should be carried out. The sensitivity testing to DAT is presented in appendix 4.

Antibiotic treatment should be administered to eliminate the organism and prevent spread. A throat and larynx culture should be collected before antibiotic treatment is started. If antibiotics have already been started then samples should still be taken. Antibiotic therapy include benzylpenicillin IV plus one of macrolides (clarithromycin, azithromycin or erythromycin). Antibiotic treatment should continue for 14 days based on local antimicrobial susceptibility testing. For azithromycin, given the long half-life, a reduced course of 7 to 10 days can be given.

Elimination of the organism should be confirmed after antibiotic treatment has been completed by obtaining nasopharyngeal and throat swabs for culture taken two cultures at least 24 hours apart or more than 24 hours after completing antibiotics with 1—2 days interval. If microbiological clearance is not achieved an additional 10 day course of antibiotics should be prescribed following discussion with local microbiologists.

SELF-CONTROL TASK

CASE 1

A 3 year-old male became acutely ill the day before yesterday. He had high-grade fever up to 39 degrees C and complained of throat pain. At the first day of disease onset he was examined by paediatrician, according to her recommendation he was given amoxicillin and a symptomatic therapy. Despite the treatment his temperature continued to rise up to 39—40 degrees C. Today's morning his mother was concerned about difficulty breathing and drooling, the child lost his appetite, refused to drink water. He was previously healthy.

On physical examination: the child appears lethargic, toxic and in severe respiratory distress. T–38.9 degrees C, P–168, BP–112/68, RR–48; throat exam is remarkable for a bright hyperemia without exudates; the child has got inspiratory stridor; intercostal retractions at rest; the lungs clear to auscultation, without wheezing; the heart tones are muffled; the abdomen is soft and painless in palpation; the liver and spleen are not enlarged; the stool is normal, he urinated less often.

Clinical blood analysis (on admission): white blood cells — 16.0×10^9/L, red blood cells — 3.95×10^{12}/L, hemoglobin — 122 g/L, eosinophils — 1 %, band neutrophils — 38 %, segmentonuclear neutrophils — 42 %, lymphocytes — 12 %, monocytes—7 %, thrombocytes — 283×10^9/L, ESR 59 mm/h.

1. Make the initial diagnosis.
2. What is the reason for severe child's condition?
3. What help is needed?
4. Make the examination plan.
5. Administer the treatment.

CASE 2

A 15-month-old baby presented to the emergency department with chief complaints of a harsh, barking cough, hoarse voice, noisy breathing. Yesterday she had a runny nose and a fever up to 38.4 degrees C. She woke up this night experiencing difficulty breathing.

On physical examination: the child is restless, she is crying, T–38.2 degrees C, P–138, RR–40, oxygen saturation 95 % in room air; exam showes a pale skin, perioral cyanosis and intercostal retractions when crying; the mucous membrane of the oropharynx is moderately hyperemic, no exudates; the lungs clear to auscultation, without wheezing; the heart tones are rhythmic; the abdomen is soft and painless in palpation; the liver and spleen are not enlarged; the stool and urination are normal.

1. Make the initial diagnosis.
2. What help is needed?
3. Administer the treatment.

CASE 3

A 3-year-old female (weight 15 kg) became ill with a body temperature spike up to 37.7 degrees C, a harsh, obsessive barking cough and hoarseness. On the next day, the cough became more frequent, less sonorous, her temperature returned to normal. On the third day of the onset of her illness, the girl did not sleep well, was irritable and refused to eat. Her mother, worried about the appearance of rapid and noisy child breathing, sought medical attention at a hospital.

On physical examination: the child has severe condition due to respiratory distress. T–36.9 degrees C, P–148, BP–108/62, RR–46. The child is very restless. The voice is aphonic, inspiratory stridor, accessory muscle use, and intercostal retractions at rest. The cough is paroxysmal, non-productive. The skin is pale, clean, acrocyanosis, the mucosa of the oropharynx is slightly hyperemic, no exudates. Capillary refill time less than 2 seconds. Small cervical lymph nodes are palpable, painless and elastic. The heart tones are muffled. The lungs clear to auscultation, without wheezing. The abdomen is soft, and painless in palpation, the liver and spleen are not enlarged. The stool and urination are normal.

Epidemiological anamnesis: one week ago her mother had fever and sore throat.

1. Make the initial diagnosis.
2. What help is needed?
3. Make the examination plan.
4. Administer the treatment.

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Westley croup severity score

Clinical feature	Assigned score	
Level of consciousness	Normal, including sleep	0
	Disoriented	5
Cyanosis	None	0
	With agitation	4
	At rest	5
Stridor	None	0
	With agitation	1
	At rest	2
Air entry	Normal	0
	Decreased	1
	Markedly decreased	2
Retractions	None	0
	Mild	1
	Moderate	2
	Severe	3

Mild croup is defined by a Westley croup score of ≤ 2. Moderate croup is defined by a Westley croup score of 3 to 7. Severe croup is defined by a Westley croup score of 8–11. A score of ≥ 12 indicates impending respiratory failure.

Differential diagnosis of croup in children

Chaca-cteristics	Viral croup (obstructive laryngot-racheitis)	Epiglottitis	Laryngeal diphtheria	Foreing body aspiration
History	Abrupt onset, most commonly at night, of a rough cough, hoarseness, and inspiratory stridor	Rapid onset and gradually progressive course over 4–12 hours	Initially slow, then sudden onset of symptoms after 2–4 days	Sudden onset, history of choking, if the initial aspiration and choking episode is not witnessed, onset of symptoms (persistent or recurrent cough) days or weeks later
General condition	No toxic appearance	Toxic appearance, child sitting on leaning forward. Respiratory distress according to the degree of obstruction	Toxic appearance in mixed types of diphtheria. Respiratory distress according to the degree of obstruction	No toxic appearance in partial airway obstruction. Respiratory distress in complete airway obstruction
Fever	Depending on aetiology: usually low-grade fever	High-grade	Varied: in isolated laryngeal diphtheria is low-grade	No fever
Cough	Barking	Absent	Barking	Choking
Voice	Hoarse	Muffled	Hoarseness or aphonia	Hoarseness or inability to speak
Dysphagia	Absent	Present	Varied: in isolated laryngeal diphtheria is absent, in combination with tonsillar diphtheria may present	Depending on location of the FB
Drooling	Absent	Present	Usually absent	Absent
X-ray findings	Steeple sign (subglottic narrowing on a frontal neck X-ray)	Thumb sign (thickening of epiglottis on a lateral neck X-ray)	Subglottic narrowing	Most FB are radiolucent
Response to cortico-steroids	Improvement	No improvement	No improvement	No improvement

Recommended antimicrobial treatment for infectious epiglottitis

Antimi-crobial agent	Dosage, route	Treatment frequency	Comment
Ceftri-axone	Neonates 0—14 days: 50 mg/kg/day IV	Once daily or in two divided doses, twice daily (12 hourly) when doses greater than 2 g daily	For children with body weight of 50 kg or more the usual adult dosage should be given
	Children 15 days to 12 years of age (<50 kg): 80—100 mg/kg/day (max 4 g) IV		
	Adults and children over 12 years of age (≥50 kg): 2—4 g per day IV		
Cefo-taxime	Neonates 0—7 days: 100 mg/kg/day IV	In two divided doses (12 hourly)	
	Children 7 days to 1 month: 150 mg/kg/day IV	In three divided doses (8 hourly)	
	Children 1 month to 12 years of age (<50 kg): 150–200 mg/kg/day (max 12 g) IV	In four divided doses (6 hourly)	
	Adults and children over 12 years of age (≥50 kg): 6–8 g per day (up to 12 g) IV	In three to four divided doses (6 to 8 hourly)	
Vanco-mycin	Children 1 month to 12 years of age: 10–15 mg/kg (max 2 g per dose) IV	Every 6 hours	
	Adults and children over 12 years of age: 15—20 mg/kg (max 2 g per dose) IV; a loading dose of 25—30 mg/kg IV can be used to facilitate rapid attainment of target trough serum vancomycin concentration	Every 8 to 12 hours	
Mero-penem	Children 3 months to 12 years of age (<50 kg): 40 mg/kg IV	Every 8 hours	For children with body weight of 50 kg or more the usual adult dosage should be given
	Adults and children over 12 years of age (≥50 kg): 2 g IV		

Sensitivity testing to diphtheria anti-toxin

In people with a negative history for animal allergy and no prior exposure to equine-derived immunoglobulin:

– Do not perform sensitivity testing and proceed with a slow IV infusion of full recommended dose.

– The anti-toxin should be mixed in 250 ml to 500 ml of normal saline and administered slowly with 10 % of volume over the first 30 minutes, and the remainder over 2 to 4 hours, with close monitoring for anaphylaxis.

In patients with a positive history for animal allergy or prior exposure to equine-derived immunoglobulin suggesting increased risk:

1. Inject ~0.05 ml of a 1 : 100 dilution of the serum (in normal saline) intradermally to cause a ~5 mm bleb, and wait 30 minutes.

2. If no evidence of hypersensitivity reaction, repeat intradermal injection using a 1 : 10 dilution of the serum (in normal saline) and wait 30 minutes.

3. If no evidence of hypersensitivity reaction (erythema, itch), proceed with a slow IV infusion of full recommended dose. The anti-toxin should be mixed in 250 ml to 500 ml of normal saline and administered slowly with 10 % of volume over the first 30 minutes, and the remainder over 2 to 4 hours, with close monitoring for anaphylaxis.

4. If intradermal testing is positive or equivocal, then the schedule of desensitisation should be followed. To dilute for intradermal testing, make serial dilutions as follows:

– 0.1 ml of serum + 0.9 ml normal saline = 1 : 10 dilution;

– 0.1 ml of 1 : 10 dilution + 0.9 ml normal saline = 1 : 100 dilution.

Recent use of an antihistamine (in last 48 to 72 hours) — including antihistamines present in over-the-counter preparations such as cough remedies — may interfere with the intradermal test. In this case, either seek the advice of a specialist in allergy to undertake screening using a positive (histamine) and negative (saline) control, or follow the desensitisation protocol for someone with a positive intradermal test.

5. Monitor the patient carefully during treatment and ensure facilities for treating anaphylaxis (including 1 : 1,000 adrenaline for injection) are readily available.

Desensitisation to DAT

Patients with positive sensitivity testing to DAT or with a previous history of adverse reaction to DAT administration (even with a negative or equivocal intradermal test) should undergo desensitization (fig.). The IV route is considered safer because it offers better control. Thirteen step doses should be administered at 15 minute intervals as shown in the figure below (desensitisation protocol).
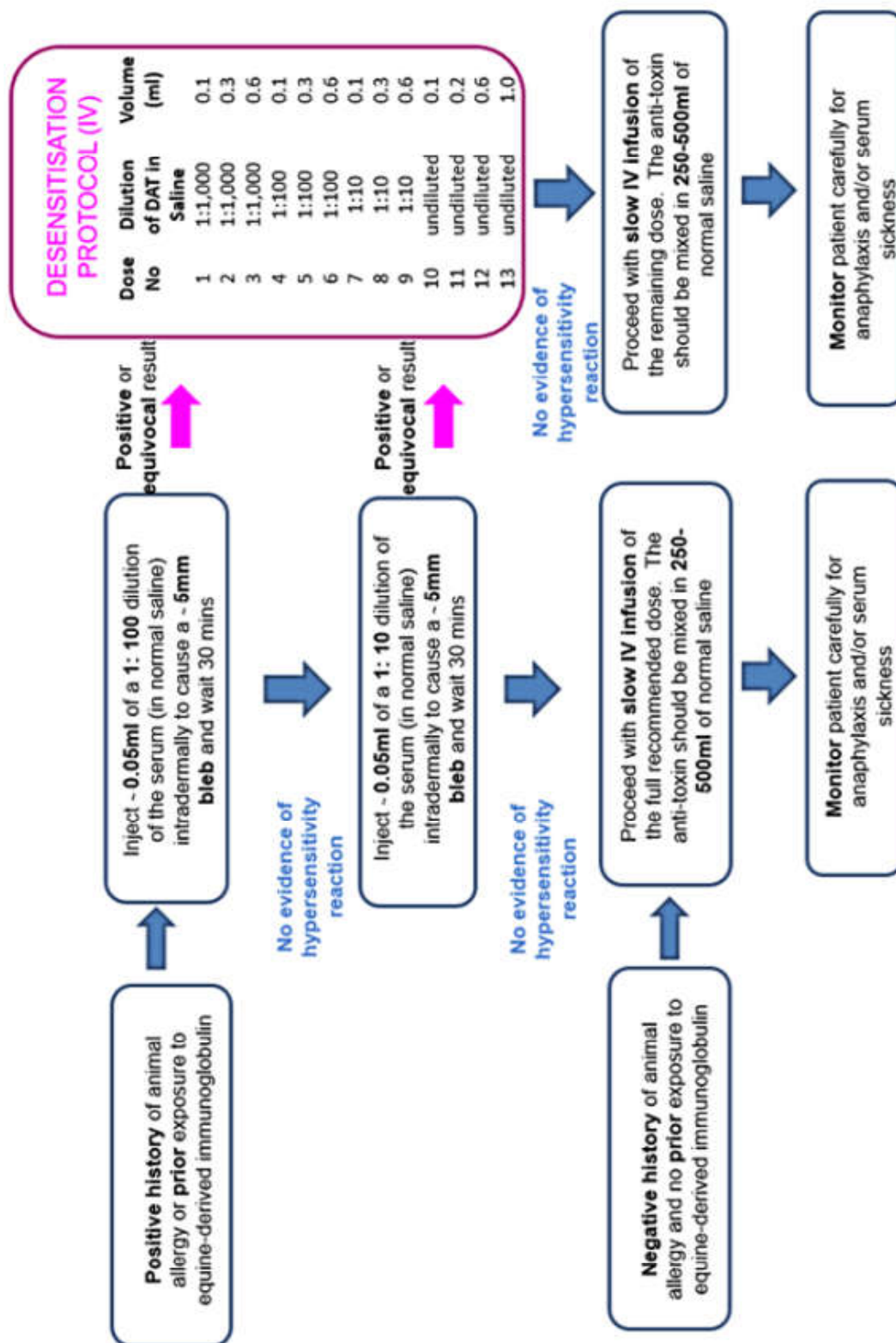
DESENSITISATION PROTOCOL (IV)

Dose No	Dilution of DAT in Saline	Volume (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	0.2
12	undiluted	0.6
13	undiluted	1.0

Positive history of animal allergy or **prior** exposure to equine-derived immunoglobulin

↓

Inject – **0.05ml** of a **1: 100** dilution of the serum (in normal saline) intradermally to cause a ~ **5mm bleb** and wait 30 mins

Positive or equivocal result →

No evidence of hypersensitivity reaction

↓

Inject – **0.05ml** of a **1: 10** dilution of the serum (in normal saline) intradermally to cause a ~ **5mm bleb** and wait 30 mins

Positive or equivocal result →

No evidence of hypersensitivity reaction

→ Proceed with **slow IV infusion** of the remaining dose. The anti-toxin should be mixed in **250-500ml** of normal saline

→ **Monitor** patient carefully for anaphylaxis and/or serum sickness

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Negative history of animal allergy and no **prior** exposure to equine-derived immunoglobulin

↑

Proceed with **slow IV infusion** of the full recommended dose. The anti-toxin should be mixed in **250-500ml** of normal saline

→ **Monitor** patient carefully for anaphylaxis and/or serum sickness

Fig. Summary of DAT administration according to patient history and sensitivity testing

To dilute for desensitization, make serial dilutions as follows:

– 1 ml (anti-toxin) + 9.0 ml of saline (sodium chloride 0.9% injection) = 1:10 dilution;

– 1 ml (1:10 dilution) + 9.0 ml of saline = 1:100 dilution;

– 0.1 ml (1:10 dilution) + 9.9 ml saline = 1:1,000 dilution;

– 1 ml (1:100 dilution) + 9 ml saline = 1:1,000 dilution.

The protection from anaphylaxis afforded by giving DAT according to this desensitisation protocol requires that no interruption occur in the sequence of administration of doses. If an interruption occurs the protection is lost. If no hypersensitivity reaction occurs, administer remaining quantity of anti-toxin.

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