PERTUSSIS.
MUMPS INFECTION

Minsk BSMU 2021

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА ДЕТСКИХ ИНФЕКЦИОННЫХ БОЛЕЗНЕЙ

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КОКЛЮШ. ПАРОТИТНАЯ ИНФЕКЦИЯ

PERTUSSIS. MUMPS INFECTION

Учебно-методическое пособие

Минск БГМУ 2021

УДК 616.921.8(075.8)-054.6
ББК 55.142я73
Р69

Рекомендовано Научно-методическим советом университета в качестве учебно-методического пособия 19.05.2021 г., протокол № 5

Рецензенты: д-р мед. наук, проф. каф. инфекционных болезней и детских инфекций Белорусской медицинской академии последипломного образования А. А. Ключарева; каф. пропедевтики детских болезней Белорусского государственного медицинского университета

Романовская, О. Ф.

Р69 Коклюш. Паротитная инфекция = Pertussis. Mumps infection : учебно-методическое пособие / О. Ф. Романовская, И. Н. Ластовка, Р. Н. Манкевич. – Минск : БГМУ, 2021. – 44 с.

ISBN 978-985-21-0903-1.

Изложены вопросы этиологии, эпидемиологии, патогенеза, клинической картины, диагностики, лечения и профилактики коклюша и паротитной инфекции у детей.

Предназначено для студентов 4-го и 6-го курсов медицинского факультета иностранных учащихся, обучающихся на английском языке.

УДК 616.921.8(075.8)-054.6
ББК 55.142я73

Учебное издание

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На английском языке

Ответственная за выпуск О. Н. Романова
Переводчики О. Ф. Романовская, И. Н. Ластовка
Компьютерная вёрстка О. В. Лавникович

Подписано в печать 16.09.21. Формат 60×84/16. Бумага писчая «Xerox office».
Ризография. Гарнитура «Times».
Усл. печ. л. 2,56. Уч.-изд. л. 2,47. Тираж 40 экз. Заказ 471.

Издатель и полиграфическое исполнение: учреждение образования
«Белорусский государственный медицинский университет».
Свидетельство о государственной регистрации издателя, изготовителя,
распространителя печатных изданий № 1/187 от 18.02.2014.
Ул. Ленинградская, 6, 220006, Минск.

ISBN 978-985-21-0903-1

ABBREVIATIONS

AGG — agglutinogen
CBC — complete blood count
CNS — central nervous system
CSF — cerebrospinal fluid
DNA — deoxyribonucleic acid
ECG — electrocardiogram
EEG — electroencephalogram
EIA — enzyme immunoassay
ELISA — enzyme-linked immunosorbent assay
ESR — erythrocyte sedimentation rate
DTaP — diphtheria-tetanus toxoids, acellular pertussis vaccine with full-strength doses
DTP vaccines — diphtheria-tetanus toxoids, acellular pertussis vaccine, adsorbed vaccines
HIV — human immunodeficiency virus
ICD — International Classification System of Diseases
IHPS — hypertrophic pyloric stenosis
IgM — immunoglobulin M
IgG — immunoglobulin G
IgA — immunoglobulin A
IV — intravenously
LPS — lipopolysaccharide
MMR — measles, mumps, and rubella
MRI — magnetic resonance imaging
MuV — mumps virus
OMP — outer membrane protein
PCR — polymerase chain reaction
PT — pertussis toxin
RBCs — red blood cells
RNA — ribonucleic acid
Tdap — diphtheria-tetanus toxoids, acellular pertussis vaccine with smaller doses of diphtheria and whooping cough
TCT — tracheal cytotoxin
WBCs — white blood cells
WHO — World Health Organization

MOTIVATIONAL CHARACTERISTICS OF TOPIC

Total in-class hours: 5.

Pertussis is the most frequent vaccine-preventable disease in children less than 5 years old in industrialized countries and has become much more prevalent over the time since the acellular pertussis vaccine replaced the whole cell biologic. Anatomical and physiological features of the respiratory and nervous systems, inadequate regulatory functions in early childhood age predispose to complicated progress of pertussis. High susceptibility of children, especially in the first few months of life, whose disease is severe and often requires an intensive care, illustrates the need for the organization of qualitative prevention. The introduction of active immunization has contributed to a sharp decline in morbidity and mortality. However, the unfavourable epidemiological situation has persisted, and in recent years the source of infection most often are teenagers and adults with erased and subclinical forms of the disease.

Mumps is an acute infectious disease, which characterized by a wide variety of clinical forms. There are involvement of different organs from slavery glands, pancreas, testes, ovaries to the meninges, which create great difficulties in diagnosis. The introduction of active immunization against mumps has reduced the incidence among children of preschool age. However, in recent years there has been an increase in the incidence of this infection among adolescents and adults. Moreover, there is a high risk of developing serious complications in the form of diabetes mellitus, chronic pancreatitis, deafness, blindness and azoospermia in cases of mumps.

In this regard, relevant questions remain for early diagnosis, therapy and prevention of pertussis and mumps. All these factors dictate the need for a detailed study of these nosologies.

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 modern diagnosis, treatment and prevention of pertussis and mumps infection, taking into accounts the features of the clinical course of the disease, depending on the child's age and reactivity.

Class tasks. The students should *know*:

– aetiology, epidemiology, classification, pathogenesis, clinical symptoms and syndromes of pertussis and mumps infection in children and adolescents;

– clinical and epidemiological directions, rules of hospitalization of children with pertussis, mumps infection and epidemiological regime (inpatient and outpatient);

– specificity of laboratory diagnosis of pertussis, mumps infection and differential diagnostics with other diseases that have similar clinical manifestations;

– the main complications and outcomes of pertussis and mumps infection, the principles of treatment in children with these diseases;

– the clinical symptoms and special characteristics of emergency conditions in children and adolescents with pertussis and mumps infection;

– the principles and methods of general and special prevention pertussis, mumps infection; vaccine schedule and organization of outpatient immunoprophylaxis.

The students should *be able to*:

– perform clinical examination of a child with pertussis, mumps infection, make the plan of examination, and identify the necessity of hospitalization of a child with these infections;

– evaluate the results of examination of patients with pertussis, mumps infection make a clinical diagnosis;

– fill in medical documents in cases of pertussis, mumps infection;

– carry out preventive measures at the site of infection.

The students should *master*:

– methods of epidemiological analysis of development of pertussis, mumps infection in children;

– methods of identifying the clinical symptoms, atypical, severe and complicated forms of infections;

– 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 pertussis, mumps infection;

– 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 glandular organs, the Central Nervous System (CNS), Respiratory System in children;

– Microbiology, Virology, Immunology: properties of the pathogens of mumps, pertussis, fundamentals of immunity;

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

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

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

– Neurology and Neurosurgery: examination methods in neurology and neurosurgery;

– Infectious Diseases: cerebrospinal fluid composition, depending on the type of inflammation;

– Urology: clinical presentations of non-mumps orchitis.

Questions for self-control from related disciplines:

1. What is the name of exoepithelial glands?
2. Give the characteristic of specific anatomical and physiological features of the respiratory system and immunological status in young children.
3. Give a description and name the main properties of mumps virus.
4. Give a comparative description of pertussis bacilli.
5. What biochemical diagnostic techniques do you know?
6. Which biological materials should be sent to a laboratory for virological, bacteriological and serological studies?

Test questions on the topic of the lesson:

1. Give a description of the causative agent of pertussis.
2. Describe the epidemiological aspects of pertussis: the source of infection, mechanisms and modes of transmission, the index of contagiousness.
3. What are the pathogenesis mechanism of the development of pertussis?
4. Give a classification of the clinical forms of pertussis.
5. What are the clinical manifestations and pathognomonic symptoms and signs of pertussis in the different periods of illness?
6. What are the complications of pertussis?
7. What methods of laboratory diagnosis of pertussis do you know?
8. What are the indications for hospitalization and the basic principles of pertussis therapy?
9. What are the methods of prevention and control measures for pertussis? What are the acellular vaccines?
10. Describe the causative agent of mumps.
11. Give a description of the epidemiological aspects of mumps: the source of the infection, mechanisms and modes of transmission, the index of contagiousness.
12. What are the pathogenesis mechanism of the development of different forms of mumps, the role of CNS impairment?
13. Give a classification of the clinical forms of mumps.
14. Describe the clinical manifestations of different forms of mumps.
15. What are the clinical signs of mumps meningitis, meningoencephalitis?
16. What are the main methods of laboratory diagnosis of mumps and their relevance depending on time from disease onset?
17. What are the indications for hospitalization and the basic principles of mumps therapy?
18. What are the methods of prevention and control measures for mumps infection?

PERTUSSIS

Pertussis (whooping cough) is a highly contagious, acute respiratory illness of humans caused by the gram-negative bacterial pathogen Bordetella pertussis (B. pertussis). In China, pertussis is referred to as the «100-day cough». Coughing can be so severe that it can result in not only vomiting, exhaustion, but subarachnoid haemorrhage in infants or hemorrhagic stroke in the elderly.

B. pertussis is a strict human pathogen with no known animal or environmental reservoir. While nine species of Bordetella have been identified to date, only three additional members, B. bronchiseptica, B. parapertussis, and B. holmesii, have been associated with respiratory infections in humans and other mammals. B. holmesii is the most frequently reported bacterium of these new species. B. holmesii causes a pertussis-like illness with milder respiratory symptoms and shorter cough duration compare with pertussis but also cases a wide range of invasive infections from bacteraemia to meningitis, endocarditis and septic shock. Although most patients with invasive B. holmesii infection had an underlying disease, severe infections have been reported in previously healthy individuals including children. B. bronchiseptica infects a wide variety of hosts and occasionally causes cough illness in humans; in particular, severe infections have been noted in persons who are immunocompromised, such as patients with Acquired immunodeficiency syndrome. Human-adapted B. parapertussis causes a milder pertussis-like disease with cough is accompanied by paroxysms in more than 70 % of the cases and by post-tussive vomiting in nearly 40 % and, like B. pertussis, lacks an environmental reservoir.

Although pertussis is relatively well-controlled at present by extensive vaccination programs, it is evident that the circulation of B. pertussis throughout the world continues largely unabated. Whooping cough is still common in areas of the world where vaccine use is low. Recent studies suggest that there are presently 48,5 million yearly cases of pertussis worldwide, with as many as 295 000 deaths.

One effect of vaccination has been a shift in the incidence of reported pertussis from children aged 1–9 years in unvaccinated populations to infants, adolescents, and adults in vaccinated populations. Reasons for this shift include incomplete immunity in infants who have received fewer than three doses of vaccine, the relatively short-lived immunity that results from vaccination, and the recent greater awareness of pertussis in adolescents and adults. Although adolescent and adult pertussis is significant in terms of medical costs and lost work, the most worrisome consequence is epidemiological. Numerous studies have shown that adults and adolescents provide a reservoir of B. pertussis and are the major source of transmission to partially immunized infants and children.

Historical background

The first mentioning of the disease was found in Moulton's The Mirror of Health, in 1540 but he also refers to a paper by Nils Rosen von Rosenstein which suggested that the illness began in France in 1414. The first epidemic was noted in Paris, France, in 1578. In 1679, Sydenham named the illness pertussis (meaning violent cough).

Bordet and Gengou reported the isolation of B. pertussis in 1906, although they had observed the organism microscopically in the sputum of a patient with pertussis in 1900.

Analysis of the genomes of 343 B. pertussis isolates from around the world over the last 100 years carried out by a multinational scientific group (published in 2014) suggests that the organism has emerged within the last 500 years, consistent with forgoing historical records.

B. parapertussis was first isolated from children with pertussis in the 1930s by Eldering, Kendrick, Bradford and Slavin.

B. bronchiseptica was first isolated during the first decade of the 20th century by Ferry, McGowan and perhaps others in studies of dogs suffering from distemper. Further studies in the early 20th century demonstrated B. bronchiseptica infections in many animals and also humans.

B. holmesii was presented as a new gram-negative species associated with septicemia in 1995. This organism was first isolated in 1983 but was not associated with respiratory illness until 1998. During the period from 1995 through 1998, B. holmesii was recovered from nasopharyngeal specimens of 33 patients in Massachusetts with pertussis-like symptoms.

Aetiology

Bordetellae are small, Gram-negative, aerobic coccobacilli. B. pertussis produces a number of virulence factors, including pertussis toxin (PT), adenylate cyclase toxin, filamentous hemagglutinin, and hemolysin. Agglutinogens and other outer membrane proteins are important antigens.

The Bordetellae are characterized by culture characteristics, biochemical tests, and nucleic acid analysis. Some of them show reversible antigenic modulation under certain culture conditions, and they mutate through several antigenically distinct phases when grown on agar.

B. pertussis is a small (approximately 0,8 μm by 0,4 μm), rod-shaped, coccoid, or ovoid Gram-negative bacterium that is encapsulated and does not produce spores. It is a strict aerobe. It is arranged singly or in small groups and is not easily distinguished from Haemophilus species. B. pertussis and B. parapertussis are

non-motile. Numerous antigens and biologically active structural components have been demonstrated in B. pertussis (fig. 1), although their exact chemical structure and location in the bacterial cell are known only in part.

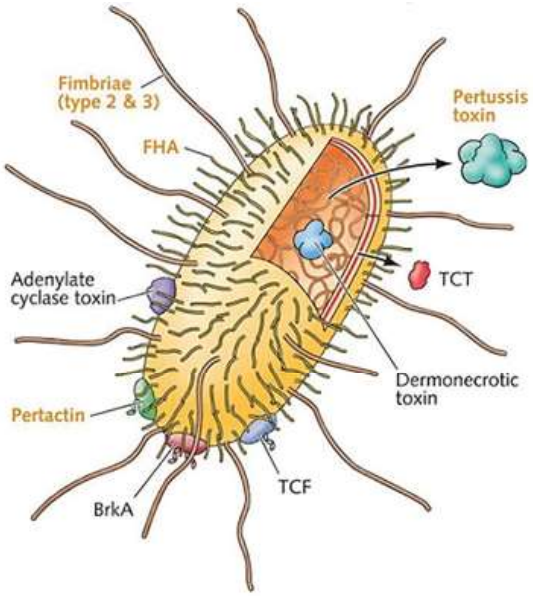

Fig. 1. Structural components of B. pertussis

One of the important factors of pathogenicity is **pertussis toxin**. Various immunologic, physiologic, and pharmacologic effects are induced by killed B. pertussis cells in experimental animals (e. g., increased sensitivity to histamine and serotonin and active and passive anaphylaxis). Adjuvant activity, leukocytosis, splenomegaly, cell proliferation, hypoglycemia, and hypoproteinemia also occur. Many additional features have been described, including increased sensitivity to factors such as endotoxins, X-irradiation, infection, cold stress, pollen extracts, peptone shock, and methacholine; increased resistance to infection; increased capillary permeability; and accelerated production of experimental «allergic» encephalomyelitis. It is now generally accepted that all those biologic activities are caused by PT.

PT is a protein exotoxin, secreted during in vivo and in vitro growth; it consists of five different subunits, designated S1, S2, S3, S4, and S5. Since the toxin molecule contains two S4 subunits, it is a hexamer. Like many other protein toxins, PT consists of an A subunit that carries the biologic activity and a B subunit that binds the complex to the cell membrane. In PT, the S 1 subunit constitutes the A protomer and the B oligomer is formed by the remaining five subunits. The toxin binds to cell receptors by two dimers, one consisting of S2 and S4 and the other of S3 and S4 (fig. 2). Since glutaraldehyde-inactivated PT is capable of adherence, this binding activity evidently has little to do with the various toxic activities of PT.

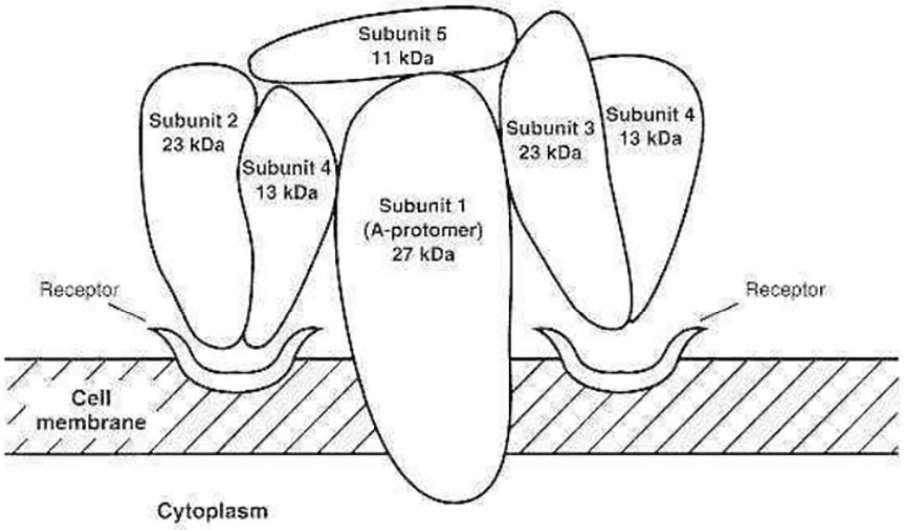

Fig. 2. Binding of pertussis toxin to cell membranes (Medical Microbiology. 4th ed. Chapter 31. Bordetella)

The toxin reacts with different cell types, including T lymphocytes, and acts on different cellular regulatory processes. PT is a member of the family of ADP-ribosylating bacterial toxins. The S1 subunit of PT ADP-ribosylates the Cys^{352} of protein Gi (GTP-binding protein), as well as the corresponding cysteine of protein Gα and of transducin. Although PT is synthesized solely by B. pertussis, both B. parapertussis and B. bronchiseptica possess genes for PT without expressing them. B. parapertussis expresses PT when the toxin gene from the B. pertussis chromosome is introduced into B. parapertussis.

PT is one of the hemagglutinins, whereas another component with hemagglutinating activity is called **filamentous hemagglutinin**. This component appears as fine filaments, about 2 nm in diameter and 40 to 100 nm in length. Like PT, it has hemagglutinating activity as well as the ability to effect the adherence of B. pertussis to cilia by its lectin-like binding to lactose-containing moieties. Filamentous hemagglutinin also performs immunomodulatory functions that contribute not only colonization, but also persistence of microorganism reducing Th1 immune response.

Adenylate cyclase toxin is a protein toxin that penetrates the host cell, activated by host cell calmodulin, and increases intracellular cyclic adenosine monophosphate (CAMP) massively. The increase of CAMP depresses phagocytic function of leukocytes inhibiting their oxidative responses and natural killer cell activity.

Lipopolysaccharide (LPS). The heat-stable Bordetella endotoxin is similar in structure, chemical composition, and biologic activity to other endotoxins produced by Gram-negative bacteria. LPS has a pronounced immunogenicity, causes a general toxic, pyrogenic action, and induction of tumors necrosis factor.

Tracheal cytotoxin (TCT) is chemically related to peptidoglycan. TCT and LPS either alone and in combination induced blebbing and necrosis of the ciliated epithelia in animal models and in human nasal biopsies. TCT and LPS induced

loss of ciliated epithelial cells and hypermucus production which interfered with mucociliary clearance.

The heat-labile toxin of Bordetella is a proteinaceous **dermonecrotic** toxin with a molecular weight of about 100 000 localized in the protoplasm. This toxin produces strong vasoconstrictive effects, which are probably important during the initial phase of pertussis by their action on the respiratory tract. Thus, heat-labile toxin, in association with TC and LPS, possibly causes tissue damage in the respiratory tract.

The agglutinogens (AGGs) are surface antigens responsible for agglutination of the bacterial cells in the presence of their corresponding antibodies. AGGs facilitate attachment to ciliary respiratory epithelium. To date, 14 different AGGs (AGG 1 through AGG 14) have been distinguished. AGG1 is specific for B. pertussis, and is associated with lipooligosaccharide. AGG 14 is thought to be specific for B. parapertussis. The AGGs 2 and 3 (formerly 2, 3, 4, 6) are associated with different types of fimbriae of B. pertussis, which may also be true for the AGGs 8, 9 and 10 of B. parapertussis.

Outer membrane proteins (OMPs). At least four different outer membrane protein structures are distinguished on B. pertussis; they are designated OMP 15, OMP 18, OMP 69, and OMP 91. They are believed to be protective antigens. OMP 69 (**pertactin**) is a 93 kDa autotransporter protein and highly immunogenic factor. Pertactin participates in attachment through its arg-gly-asp motif to facilitate eukaryotic cell binding and invasion. Antibodies are found to it after natural disease and immunization with vaccines containing this protein.

Epidemiology

Pertussis is highly communicable infection. The index of contagiousness is 70–90 %, and in unvaccinated children it is close to 100 %. Patients are infectious just prior to and for 21 days after the onset of cough, when treated with a macrolide antibiotic, the period of infectivity usually lasts 5 days or fewer after therapy starts. The duration of the infectious period depends on patient age, vaccinated status, so in vaccinated children it is usually no more than 2 weeks.

The mechanism of pertussis transmission is droplet. Vection occurs by close contact with cases via large respiratory droplets generated by coughing or sneezing. The source of infection are cases (children, adults) with both typical and atypical forms. Pertussis occur year-round, typically with a late summer-autumn peak. Neither infection nor immunization provides lifelong immunity. Waning immunity, particularly when acellular pertussis vaccine is used for the entire immunization series, is predominantly responsible for increased cases reported in school-aged children, adolescents, and adults. Siblings and adults with cough illness are important sources of pertussis infection for young infants.

Globally, 20–40 million cases of pertussis occur each year, 90 % of which are in developing countries. The World Health Organization (WHO) recommended that a pertussis incidence of < 1 case per 100 000 population be achieved in Europe by 2000. Available data from countries indicate that this goal has not been achieved in Europe, and only Japan has reached this target. Other countries with low reported national incidences (cases per 100 000 population) include Spain, the United States, France and the United Kingdom. Conversely, the highest incidences (cases per 100 000 population) were reported worldwide from Australia and Switzerland. Possible reasons include differences bioevolution in laboratory confirmation, reporting and surveillance of pertussis, of the circulating organism and the various immunization strategies and target groups present in the different countries.

Despite high immunization rates in infants and children in many coun-tries, pertussis remains endemic, with epidemics superimposed every 2–5 years. It has remained unchanged from the pre-vaccination era and is probably caused by continued transmission of pertussis among adolescents and adults, with passage to susceptible infants. However, even though the epidemic cycle seems to have become less distinct, pertussis disease continues to remain a problem especially in the young infant population younger than 3 months of age.

The incidence of pertussis in older age groups has been increasing in a number of countries in recent years. During the 1990s, the annual number of reported pertussis cases in the United States varied between 5000 and 8000, with large outbreaks occurring every 3–4 years. When comparing the number of cases in the various groups during the period from 1990–1993 with the period from 1996 to 2000, the incidence of pertussis in the 10- to 19-year group was noted to increase by > 100 %; whereas the incidence in the ≥ 20-year group increased by almost 95 %. These data indicate that the most significant increase in pertussis disease has been seen among the adolescent and adult populations (fig. 3).

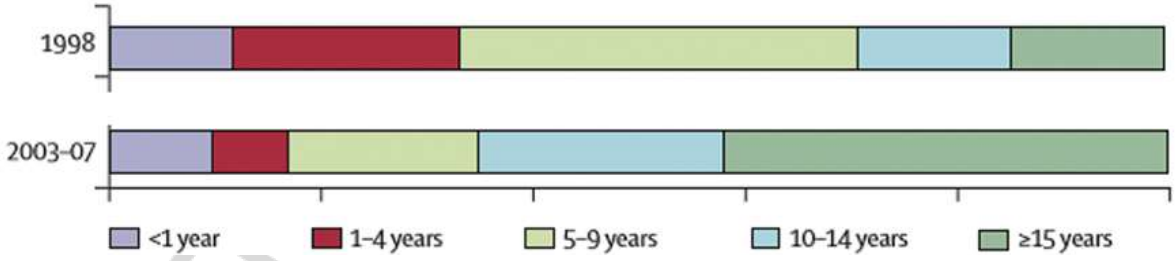

Fig. 3. Age structure of pertussis cases in Europe

Immunity. A case of whooping cough confers substantial immunity, which usually lasts for many years. Second infections of adults, usually with atypical symptoms and thus not regularly diagnosed as pertussis, may be more frequent than previously assumed. Immunity acquired after infection with B. pertussis does not protect against the other Bordetella species.

PT is assumed to be one essential protective immunogen, but numerous findings indicate that other components, such as filamentous hemagglutinin, heat-labile toxin, AGGs, OMPs, and adenylate cyclase toxin, may also contribute to immunity after infection or vaccination. The immunogenicity of the substances may be significantly increased by the presence of PT. This synergism indicates that PT could function as an adjuvant to a variety of protective antigens of B. pertussis. The defense mechanisms are both nonspecific (local inflammation, increase in macrophage activity, and production of interferon) and specific (proliferation of B and T cells). The basis of immunity in whooping cough is, however, incompletely understood. A role of circulating antibody in immunity is indicated by the correlation between protection of human vaccines and their serum agglutinin titers. However, effective immunity does not necessarily depend on the presence of serum agglutinins, and immunity to whooping cough may therefore be mediated essentially by cellular mechanisms. This cell-mediated immunity may be considered the crucial carrier of long-term immunity, and titers of specific humoral antibodies may diminish over the years. This may be the reason why infants usually do not benefit significantly from maternal antibody.

Pathogenesis

Whooping cough infection results in colonization and rapid multiplication of the bacteria on the mucous membranes of the respiratory tract. Bacteremia does not occur. B. pertussis adheres only to the tuft of ciliated cells in the mucosa of the human respiratory tract; no attachment to nonciliated cells is observed. The adherence of pathogen to human cilia is effected by a synergistic action of PT and filamentous hemagglutinin, each acting as a bivalent bridge between the bacterium and the ciliary receptor.

Studies of numerous B. PTs and their corresponding biologic activities have yielded plausible explanations for many of the symptoms of whooping cough. These include, for example, the frequent occurrence of absolute lymphocytosis (an unusual phenomenon in bacterial infections), hypoglycemia, and the adjuvant effect of PT on the immune response to unrelated antigens. The finding that phase I isolates of B. bronchiseptica (depending on the differences in the antigenic structure of Bordetella, several phases are distinguished) produce almost complete ciliostasis within 3 hours in ciliated epithelial cell outgrowths from canine tracheal explants may be explained by the action of adenylate cyclase toxin and TCT. The same toxins evidently inhibit the phagocytic activities of the host. In humans, an initial local peribronchial lymphoid hyperplasia occurs, accompanied or followed by necrotizing inflammation and leukocyte infiltration in parts of the larynx, trachea, and bronchi. Usually, peribronchiolitis and variable patterns of atelectasis and emphysema also develop.

To date, there is no plausible explanation for the development of the paroxysmal coughing syndrome characteristic of pertussis. According to Pittman, pertussis is mediated by PT and is characterized by a two-stage process — colonization and disease — thus resembling other bacterial toxicoses such as diphtheria, tetanus, and cholera. This fascinating idea can be accepted only if it is clearly demonstrated that PT causes paroxysmal coughing. Such a demonstration is lacking. Moreover, paroxysmal coughing occurs in infections with B. parapertussis, which does not synthesize PT. On the other hand, an additional infection with B. pertussis cannot be excluded in such cases.

Research into the pathogenetic mechanisms of pertussis are hampered by the lack of an adequate animal model showing the characteristic paroxysmal coughing syndrome and by the limited opportunity to perform direct studies of the respiratory tract of babies and children.

Classification of pertussis

In the clinical classification of whooping cough, the following forms are distinguished:

1) typical;
2) atypical, which are presented by next forms:
– inapparent;
– subclinical;
– abortive;
– transient bacteria carrying.

Classification of pertussis in ICD-11 for Mortality and Morbidity Statistics includes:

1C12 Whooping cough
1C12.0 Whooping cough due to Bordetella pertussis
1C12.1 Whooping cough due to Bordetella parapertussis
1C12.Y Other specified whooping cough
1C12.Z Whooping cough, unspecified.

Clinical features

The incubation period of whooping cough ranges from 3 to 21 days, and rarely may be as long as 42 days. After the incubation period, pertussis infection typically progresses through three distinct stages (fig. 4):

1. Catarrhal
2. Paroxysmal
3. Convalescent

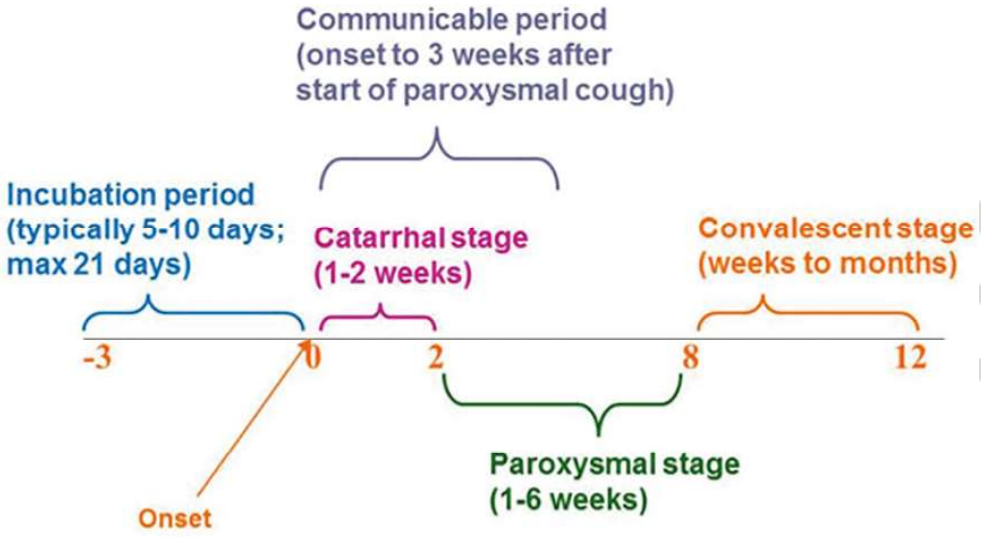

Fig. 4. Clinical course of pertussis (in weeks)

The catarrhal stage. Pertussis symptoms usually develop within 5 to 10 days after exposure, but usually not for as long as 3 weeks. Pertussis has an insidious onset with catarrhal symptoms that are indistinguishable from those of minor respiratory tract infections: malaise, acute coryza, sneezing, mild cough. Some affected children may experience a low-grade fever. Toward the end of this stage the cough, which is initially non-productive, intermittent, despite a treatment becomes severe, paroxysmal, especially at night.

The catarrhal stage lasts up to 2 weeks, has shorter duration in the unvaccinated and young children.

The paroxysmal stage of pertussis is characterized by recurring intense episodes of coughing. An episode or «paroxysm» consists of a series of coughs in rapid succession with increasing intensity. The last cough in the series is followed by a large inspiration that produces a characteristic «whoop» sound. During these coughing episodes, affected individuals find it difficult to draw air into the lungs (inspiration) between coughs. Typically, people with pertussis cough up (expectorate) large amounts of thick mucus, which may cause vomiting (post-pertussis emesis). Other symptoms during an attack may include bulging eyes, prominent veins in the neck, protrusion of the tongue, and/or excessive salivation.

The illness can be milder and the characteristic paroxysmal cough and «whoop» may be absent in children, adolescents, and adults who were previously vaccinated.

The convalescent stage of pertussis begins approximately 4 weeks after onset of the disease. Episodes of coughing become less frequent and not as severe. Slow recovery begins during this phase of the disease. Occasionally episodes of coughing may recur for months in intercurrent respiratory infections. Coughing attacks can also be triggered by physical or emotional stress.

The atypical forms. The atypical forms are more common in adults and vaccinated children. *The inapparent (asymptomatic) form* is not accompanied by any clinical signs and can be only laboratory confirmed by production of the immune response. *The subclinical form* is characterized by persistent throat irritation or semicough, obsessive non-productive cough, which intensify in the second week of illness, nonetheless paroxysmal cough is absent. In *the abortive whooping cough*, the beginning of disease is typical, but the resolution of convulsive cough is usually rapid, takes a week. The *transient bacteria carrying* is a positive culture or a genome of B. pertussis in the absence of clinical manifestations of illness and without increased antibody titers in paired sera. Bordetella pertussis carriage in children is occurs rare (in 1–2 % of cases), generally in vaccinated children.

The clinical features of whooping cough in unvaccinated infants

The incubation and catarrhal stages are cut to 1–2 days, the paroxysmal period is lengthened up to 6–8 weeks. Moderate and severe forms of pertussis are prevalent. Younger children with whooping cough may lack the characteristic clinical manifestations of pertussis. Coughing fits may be typical, however, whoops and tongue protrusions are less common and indistinctly expressed. In newborns cough is weak, sporadic, without whoops and a flushing face, but with cyanosis of the nasolabial triangle. But they do have paroxysms of coughing.

Vomiting and exhaustion commonly follow the episodes. They feel unwell in attack-free period. Babies may also have sneezing, unmotivated crying, screaming instead of typical coughing attacks.

Abnormalities in respiratory rhythm (breath-holding and interruption of breathing) can occur both during a coughing attack, and not in attack (in a dream, after eating). Whooping cough apnea observed in the first months of life infants is of two types: apnea during a coughing fit, lasting from 30 seconds to1 min and paralytic apnea, which is not associated with a pertussis cough. Suddenly a child becomes lethargic, hypotonic. Skin pallor first appears, and then cyanosis. Paralytic apnea lasts 1 to 2 minutes.

The clinical features of whooping cough in vaccinated children

The course of disease is usually mild or moderate whithout any complications. The atypical forms are predominated. The incubation and catarrhal period are lengthened to 2–3 weeks, the period of paroxysmal cough is shortened to 2 weeks. Such characteristic symptoms as post-tussive vomiting, whoops are less common. Complete Blood Count (CBC) may not reveal whatever changes or only relative lymphocytosis.

Complications

Complications of whooping cough mainly appear in the paroxysmal stage of the disease. Infants are more likely to have complications than older children or adults.

The coughing associated with pertussis may cause a sudden increase in the pressure within the blood vessels of the nose and/or eyes. This may lead to epistaxis and scleral hemorrhage. Aspiration of mucous into the lungs may cause bacterial pneumonia. Otitis media, pneumonia may also occur due to a secondary immunodeficiency caused by B. pertussis.

Other more severe complications may include seizures, atelectasis, bronchiectasis, refractory pulmonary hypertension, subcutaneous emphysema, encephalopathy, subarachnoid and intraventricular haemorrhage, subdural hematomas, inguinal hernia, and rectal prolapse.

Diagnosis

The WHO established the definition for pertussis.

Suspected case definition. ***A suspected case*** is a person of any age with a cough lasting ≥ 2 weeks, or of any duration in an infant or any person in an outbreak setting, without a more likely diagnosis and with at least one of the following symptoms, based on observation or parental report:

– paroxysms (fits) of coughing;
– inspiratory whooping;
– post-tussive vomiting, or vomiting without other apparent;
– apnea (only in < 1 year of age);

OR

– clinician suspicion of pertussis.

Confirmed case definition. A confirmed case of pertussis may be determined by laboratory confirmation or epidemiological linkage.

A laboratory-confirmed case is a person who meets the suspected case definition with laboratory confirmation by one of the following:

– isolation of B. pertussis;

OR

– detection of genomic sequences of B. pertussis by means of Polymerase chain reaction (PCR) assay;

OR

– elevated IgG antibodies to PT in an individual ≥ 11 years of age, one year or longer after last vaccine dose.

Epidemiologically linked. An epidemiologically linked case is a person meeting the suspected case definition with close contact to a laboratory-confirmed

case (or another epidemiologically linked case in an outbreak setting) in the three weeks prior to onset of cough.

Close contact is defined as having face-to-face exposure to a case, which includes household or family contact, people having stayed overnight in the same room with a case, and people having direct contact with respiratory, oral or nasal secretions with a laboratory-confirmed case.

Possible. A person who meets the suspected case definition but does not meet confirmed classification as defined above should be considered a possible case. This includes suspected cases who did not have laboratory testing done and those who tested negative.

Laboratory diagnostic methods of pertussis

Culture is considered the gold standard laboratory test and is the most specific of the laboratory tests for pertussis. However, fastidious growth requirements make B. pertussis difficult to culture. The yield of culture can be affected by specimen collection, transportation, and isolation techniques. Specimens from the posterior nasopharynx, not the throat, should be obtained using polyester, rayon, nylon, or calcium alginate (not cotton) swabs. Isolation rates are highest during the first 2 weeks of illness (catarrhal and early paroxysmal stages).

Cultures are less likely to be positive if performed later in the course of illness (more than 2 weeks after cough onset) or on specimens from persons who have received antibiotics or who have been vaccinated. Since adolescents and adults have often been coughing for several weeks before they seek medical attention, it is often too late for culture to be useful.

PCR is a rapid test and has excellent sensitivity. PCR tests vary in specificity, so obtaining culture confirmation of pertussis for at least one possible case is recommended any time there is suspicion of a pertussis outbreak. Results should be interpreted along with the clinical symptoms and epidemiological information.

PCR should be performed on nasopharyngeal specimens taken at 0 to 3 weeks following cough onset but may provide accurate results for up to 4 weeks of cough in infants or unvaccinated persons. After the fourth week of cough, the amount of bacterial DNA rapidly diminishes, which increases the risk of obtaining false negative results. False positive results may be obtained because of contamination in the laboratory or during specimen collection.

Serologic testing. Research has shown that measuring IgG antibody titers to PT is the most specific and sensitive assay. Serology based on other pertussis antigens should be avoided. Unlike with other diseases, IgM antibody is not used to diagnose pertussis cases due to a lack of adequate sensitivity and specificity.

Single serum should be considered positive in combination with clinically suspected pertussis. IgG is present from 4–12 weeks after cough onset. Serology is unreliable in infants due to presence of maternal antibodies, and is insensitive in

children ≤ 10 years old. Moreover, serology should not be done if pertussis vaccination occurred within the past year among persons of all ages due to presence of vaccine-induced IgG.

In the absence of recent immunization, an elevated serum IgG antibody to PT present 2 to 8 weeks after onset of cough is suggestive of recent B. pertussis infection. For single serum specimens, an IgG anti-PT value of approximately 100 IU/mL or greater (using standard reference sera as a comparator) has been recommended.

The optimal time for serological diagnosis is from third to sixth week after disease onset. For confirming infection detection of fourfold rise in IgG anti-PT in paired sera conducted 2–4 weeks apart is recommended by the WHO.

IgA and IgM assays lack adequate sensitivity and specificity and should not be used in the diagnosis of pertussis.

CBC. An elevated WBC count with a lymphocytosis at normal ESR level is usually present in classical pertussis among infants. The absolute lymphocyte count often reaches 20 000 or greater. However, there may be no lymphocytosis in some infants and children or in persons with mild or modified cases of pertussis. Lymphocytosis and thrombocytosis in young infants parallel the severity of illness. Vaccinated children may have absolute monocytosis.

Differential diagnosis of pertussis

The absence of fever during the course of illness, the characteristic whoops during coughing attacks, a change in the nature of cough from rare dry to obsessive spasmodic, despite the conducted treatment, are clinical clues for the differential diagnosis of pertussis and other respiratory diseases.

The main differential diagnoses to consider in a child presenting with a paroxysmal cough are listed below, with key features that increase the likelihood of each diagnosis in bullet points beneath:

1. Bronchiolitis/viral respiratory infection:
– acute history;
– wheeze and / or crackles (absent in pertussis);
– age under 1 year.
2. Mycoplasma pneumonia / Chlamydia pneumonia:
– chest signs: Wheeze and / or crackles (absent in pertussis);
– no lymphocytosis and usually a normal white cell count;
– ELISA confirmation.
3. Bacterial pneumonia:
– acute onset of the disease with high temperature;
– local wheezing in the lungs;
– chest signs: Focal crackles.

4. Asthma:
– chronic night time cough, or exercise-induced cough;
– recurrent episodes of breathlessness or wheeze (absent in pertussis);
– personal or family history of atopy, eg. eczema, hay fever or asthma;
– management and treatment.

Management and treatment

Macrolides erythromycin, clarithromycin, and azithromycin are preferred for the treatment of pertussis in persons 1 month of age and older. For infants younger than 1 month of age, macrolides should be used with caution as an association between orally administered erythromycin and azithromycin with infantile hypertrophic pyloric stenosis (IHPS) has been reported. However, azithromycin remains the drug of choice for treatment or prophylaxis of pertussis in very young infants because the risk of developing severe pertussis and life-threatening complications outweigh the potential risk of IHPS. Clinicians should monitor infants younger than 1 month of age who receive a macrolide for the development of IHPS and for other serious adverse events. For persons 2 months of age and older, an alternative to macrolides is trimethoprim-sulfamethoxazole.

Antibiotic effect on the duration or severity of disease is maximal when started in the catarrhal stage, and not proven effective when started in the paroxysmal stage. The primary goal of antibiotic treatment is to decrease carriage and spread of disease. Recommended antimicrobial treatment, by age group, presents in appendix 1.

Seriously ill infants with pertussis should be kept in a dark and quiet room. They should be disturbed as little as possible to help prevent frequent episodes of severe coughing. Close attention should be paid to the nutritional needs of the infant, since poor nutrition can contribute significantly to complications. Small meals should be given as frequently as possible. A cough suppressant such as butamirate citrate may be used to relieve non-productive cough. Mucolytics (acetylcysteine, ambroxol) can be used in patients with thick mucus. However, it is recommended to avoid the simultaneous use of antitussives and mucolytics.

Corticosteroids have not shown definite benefit in reducing severity and course of illness, but are sometimes given to critically ill infants.

Hospitalization may be required for seriously ill infants with pertussis or in complicated cases. Parenteral fluid therapy may be needed to replace salt and water loss if vomiting is severe. Careful suctioning of the throat may become necessary to clear excessive mucous secretions. Oxygen mask or nasal cannulas may be recommended to affected children during coughing attacks.

Prevention

The most important way to prevent pertussis is through complete immunization.

The specific prevention of whooping cough. Two types of pertussis vaccines have been developed: whole-cell (wP) and acellular (aP). Firstly it was whole-cell vaccine consisted of inactivated cells of B. pertussis. But later because of the high number of adverse reactions after wP vaccination, acellular pertussis vaccines have been created. The introduced aP vaccines composed of one to five highly purified antigens (PT, pertactin, fimbriae, adenylate cyclase etc.), were less reactogenic and offered protective immunity in first 6 years of life.

Nevertheless, in spite of worldwide vaccination the disease is still not under control and today is the most prevalent vaccine-preventable childhood disease. The reason of it is multifactorial, with improved diagnostics, enhanced surveillance, and the switch from wP to aP vaccines but also changes in genetic composition of pertussis strains (the emergence of strains with increased PT production, circulation of isolates not expressing virulence factors which are part of used vaccines) and especially rapidly waning immunity after aP vaccination or even after natural infection.

The vaccine for pertussis is usually given in combination with diphtheria and tetanus. A primary course of three doses of DTaP (diphtheria, tetanus, acellular pertussis) vaccine or DTwP (diphtheria, tetanus, whole-cell pertussis) vaccine is usually given between two and twelve months of age. A fourth dose is recommended at 11–24 months of age and another dose between three and six years of age. There is considerable variation between national immunization schedules in the timing of these doses. Some countries recommend boosters for adolescents, during pregnancy or soon after delivery. Some countries recommend boosters for adolescents, during pregnancy or soon after delivery. Passive infant immunization through vaccination of pregnant women against pertussis is crucial importance. First was introduced in 2011 in the United States and since then it has been spread to more than 40 countries.

Babies and children younger than 7 years old receive DTaP, while older children and adults receive Tdap. Tdap vaccines, contain reduced quantities of diphtheria toxoid and some pertussis antigens compared with DTaP. DTaP products may be formulated as combination vaccines containing one or more of inactivated poliovirus vaccine, hepatitis B vaccine, and Haemophilus influenzae type b vaccine.

We point to as a spectacular example is *the Pertussis Immunization Schedule in the United States*. The Center for Disease Control and Prevention (CDC) recommends whooping cough vaccination for all babies and children, preteens and teens,

and pregnant women. Adults who have never received a dose of Tdap should also get vaccinated against pertussis.

Recommendations for Routine Childhood Immunization with DTaP. Five doses of pertussis-containing vaccine are recommended prior to entering school: 4 doses of DTaP before 2 years of age and 1 dose of DTaP before school entry. The first dose of DTaP may be administered as early as 6 weeks of age, followed by 2 additional doses at intervals of approximately 2 months. The fourth dose of DTaP is recommended at 15 through 18 months of age, and the fifth dose of DTaP is administered before school entry (kindergarten or elementary school) at 4 through 6 years of age. The fourth dose can be administered as early as 12 months of age, provided 6 months have elapsed since the third dose was administered. If the fourth dose of pertussis vaccine is delayed until after the fourth birthday, the fifth dose is not recommended.

Recommendations for Routine Adolescent Immunization with Tdap. Adolescents 10 years and older should receive a single dose of Tdap instead of Td for booster immunization against tetanus, diphtheria, and pertussis. The preferred age for Tdap immunizations is 11 through 12 years of age. Adolescents who received Td but not Tdap should receive a single dose of Tdap to provide protection against pertussis regardless of time since receipt of Td. Inadvertent administration of DTaP instead of Tdap in people 7 years and older is counted as a valid dose of Tdap. Outside of pregnancy, a second dose of Tdap is not recommended.

Use of Tdap in Pregnancy. The Advisory Committee on Immunization Practices (ACIP) recommends that a dose of Tdap be administered during each pregnancy, irrespective of the mother's prior history of receiving Tdap. Tdap should be administered preferably early in the interval between 27 and 36 weeks' gestation, although Tdap may be administered at any time during pregnancy. Current evidence suggests that immunization early in the interval between 27 and 36 weeks' gestation will maximize passive antibody transfer to the infant. For women not previously vaccinated with Tdap and in whom Tdap was not administered during pregnancy, Tdap should be administered immediately postpartum. Postpartum Tdap is not recommended for women who previously received Tdap at any time.

The nonspecific prevention of pertussis at the site of infection includes:

1. Isolation of patients with droplet precautions for 21 days from onset of cough if appropriate antimicrobial therapy is not administered or for 5 days after initiation of effective therapy.

2. Notifications about all clinical suspected cases to the local public health agency (pertussis is a nationally notifiable disease).

3. Post-exposure prophylaxis with macrolides for all household contacts (appendix 1). The duration of antibiotic prophylaxis is corresponds to the duration of antibiotic therapy.

MUMPS INFECTION

Mumps infection is an acute infectious disease caused by the mumps virus (MuV), which primarily affects the salivary glands, frequently involves the central nervous system (CNS) and other organ systems in the pathological process. Since mumps is a highly contagious disease, it is also called infectious (epidemic) parotitis. Prior to the introduction of routine vaccination, MuV was a leading cause of aseptic meningitis and viral encephalitis in children in many countries.

Despite the fact that mumps was one of the most common childhood infections, due to widespread immunization over the last 20 years its incidence has dropped dramatically. Mumps is currently a rare disease, and noticed mainly among adults during outbreaks.

Nevertheless, recent mumps outbreaks involving highly vaccinated populations have prompted reevaluation of current strategies for mumps prevention.

Historical background

Mumps infection is one of the oldest recognized disease. The first written description of mumps as a disease can be found as far back as the 5th century BC. Hippocrates described an outbreak of mumps on the Greek island of Thasos, which modern physicians today still refer back to as a masterful documentation of the disease.

While various studies into the disease had been carried out across the 19th and 20th centuries, the viral aetiology of mumps was finally discovered and documented by American scientists Claud D. Johnson and Ernest W. Goodpasture in 1934. They managed to reproduce acute non-suppurative parotitis analogous to mumps in the rhesus monkeys by inoculating saliva samples from patients in the early stages of mumps (fig. 5). That filterable cytotropic virus was not found in normal saliva and did not correspond to any known viruses with which they were familiar. They admitted that the virus was the causative agent of mumps.

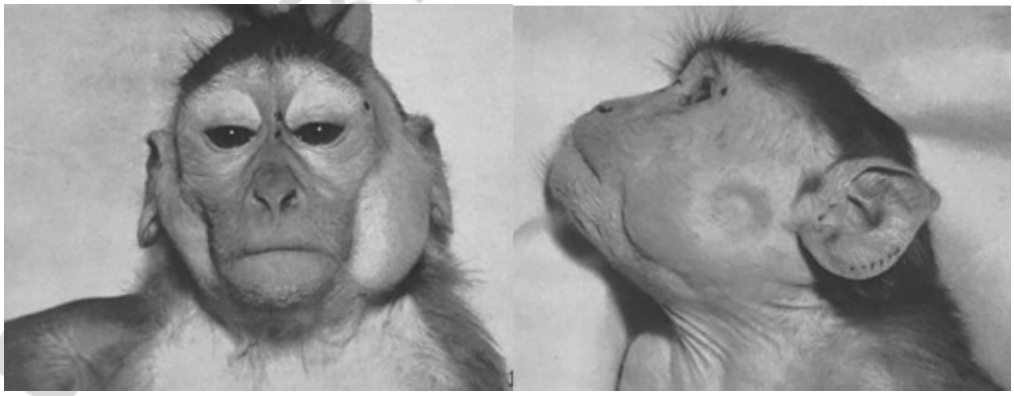

Fig. 5. An investigation of the etiology of mumps (by the Rockefeller Institute for Medical Research New York, 1934)

«During World War I, mumps was the leading cause of missed days of active duty for the US army in France and reached a total of 230 356 cases. By World War II, the threat from mumps and measles was serious enough that the military's Office of Scientific Research and Development treated it as a national security issue. After the World War II was over, illnesses like pneumonia and influenza, it was thought to be a much bigger concern. Parents did not like when they are kids got mumps, but was considered an expected part of childhood» (historian Elena Conis).

In Boston in 1945 the MuV was first isolated at autopsy of patient with Sturge-Weber syndrome and pneumonia that died with a concurrent mumps infection by Thomas H. Weller and John M. Graig.

In 1946 an American immunologist Karl Habel produced the very first experimental mumps vaccine, which was «inactivated». That vaccine was tested on 2 825 West Indian workers at a Florida sugarcane plantation where mumps ran rampant, and it showed a 58 % effectiveness against the virus. Later, however, it was discontinued because immunity was short-lived.

Since then numerous mumps vaccine strains have been developed and used in vaccines throughout the world. Most European countries have had routine childhood mumps immunization since the 1980s.

Aetiology

Mumps is caused by the MuV, a member of the genus Rubilavirus, that belongs to the Paramyxoviridae family (appendix 2). The Paramyxoviridae are widely distributed pathogens, which are among the commonest aetiological agents of respiratory infections, causing high morbidity and mortality worldwide.

The MuV is a single stranded, non-segmented negative RNA (-RNA) virus, having seven structural proteins (fig. 6). The viral genome is consisted of 15 384 nucleotides. Its virion is composed of lipoprotein envelope with three glycoproteins: hemagglutinin-neuraminidase (HN), fusion protein (F) and small hydrophobic protein (SH). Below the inner envelope surface, there is matrix protein (M). Within the virion, there is a helical nucleocapsid (viral RNA in complex with nucleoprotein (NP)) to which phosphoprotein (P) and large protein (L) are attached. L protein is RNA-dependent RNA-polymerase. The HN glycoprotein plays a major role in cell infection by the virus as it binds to sialic acid in host cell membranes thereby bringing about viral attachment, which is followed by membrane fusion through F protein and release of the viral nucleocapsid into the host cell. Neutralizing antibodies are produced notably to the HN and F protein.

The MuV as well as other RNA viruses possesses genetic diversity. The most variable part of the MuV genome is the gene for the SH protein. Based on the gene sequences for the SH and HN proteins, the MuV has been classified into

twelve genotypes (A, B, C, D, F, G, H, I, J, K, L, N). Despite existence of various genotypes, there is only one serotype. Antibody generated in response to infection with one strain of the virus can recognize the most genetically divergent strains. Genotypes show nucleotide variation of 2 to 4 % within genotypes, and 6 to 19 % between genotypes. Recently mumps genotype G viruses are the most widespread, and as well as are more frequent founded during large outbreaks.

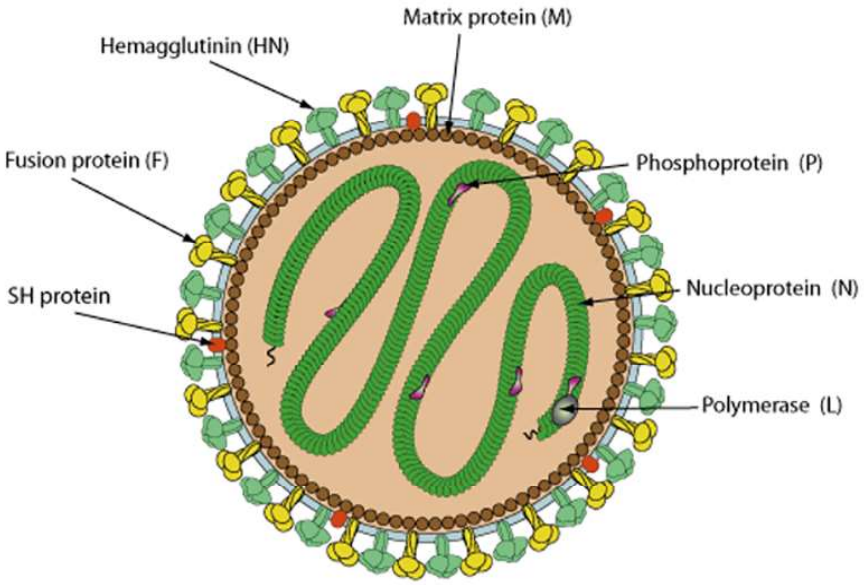

Fig. 6. Structure of mumps virus

The MuV can be isolated from the saliva, cerebrospinal fluid (CSF), urine, blood, semen, breastmilk, and infected tissues of patients with mumps (bone marrow, salivary, pancreas, testicular tissue), and can be grown in many cultures of human, monkey tissues and in embryonated eggs.

The virus is unstable in the environment and rapidly inactivated by chemical and physical agents such as formalin, chloroform, heat, ultraviolet light, but it is resistant to the action of low temperatures.

EPIDEMIOLOGY

Mumps infection occurs worldwide. Despite being considered primarily a childhood illness, mumps can affect people of all ages. In pre-vaccination era most (> 90 %) of children experienced mumps by age 20. Typically, there were epidemic periods every two to five years with children aged five to nine years most affected. Mumps infection was extremely rare in infants.

The incidence of mumps infection declined sharply after introduction of mumps vaccine globally. The first dose of vaccination decreased the incidence of mumps by 88–98 %, and the booster dose decreased the incidence by 97–99 %. For

example, the number of reported mumps cases in the United States has decreased more than 99 % since licensure of the mumps vaccine in 1967.

In the temperate climate the majority of mumps cases are seen in late winter and early spring. The number of illnesses significantly decreases in the middle of summer and increases again at the end of autumn. The converse situation is observed in Asia: a higher risk for mumps infections is during the summer months than during other seasons.

Mumps is highly communicable disease with index of contagiousness about 50–90 %. Humans are the only natural host for the MuV. Infected individuals with manifest or asymptomatic disease are the source of infection. The mechanism of transmission is airborne via droplets of saliva or mucus of an infected person, that are spreading by talking, coughing, sneezing. The MuV does not spread beyond 1 to 2 meters. Mumps may also be transmit indirectly by contact mechanism with contaminated objects. Sufferers with mumps are the most infectious from the last 2 days of the incubation period up to 5th day of disease onset.

The risk of infection is augmented by close and prolonged contact with infected individuals, so mumps infection frequently occurs in crowded population centers, e. g., prisons, kindergartens, boarding schools, summer camps, military barracks, and other similar crowded settings. Additional risk factors in mumps infection include age, compromised immunity, and vaccination status (e. g. being unvaccinated or only having received one lifetime dose of measles, mumps and rubella (MMR) vaccine). Although there is no evidence of a difference on occurrence of mumps infections between the sexes, males seemly have higher risk to present complications.

Immunity after natural infection. The previous disease leads to the formation of long-lasting immunity. Twenty or more years after their mumps illness, most individuals (82 %) still have detectable haemagglutination-inhibiting antibodies. However, second occurrences of mumps might be rarely occurred.

In unvaccinated individuals with mumps infection IgM antibodies are measurable within a few days of symptom onset. IgM peaks about one week after the onset of parotitis or symptoms, and is detectable for weeks to months after parotitis onset. Low avidity IgG may also be present at the time of symptom onset, although generally at a low level. IgG antibody increases rapidly and reaches maximum levels about three weeks after onset of symptoms. IgG antibodies remain at that level for about two to three months before they decrease again, and have been assumed to persist for life. Mumps-specific salivary IgA antibodies can be detected up to five weeks after onset of illness before gradually decreasing, becoming undetectable around 10 weeks after onset.

Maternal antibodies (IgG) to mumps following natural infection are transferred across the placenta and are believed to provide protection to infants against clinical mumps.

Immunity after vaccination. In general, over 90 % of infants and children develop detectable antibodies against mumps following vaccination with mumps vaccines. Seroconversion rates vary widely from 35 to 100 % depending on a vaccine strain. There is no difference in seroconversion between monovalent, bivalent, trivalent, or tetravalent formulations of the mumps vaccine. Vaccination with the mumps vaccine induces relatively low levels of antibodies compared with natural infection.

Studies indicate that one dose of MMR vaccine can provide persistent antibodies to mumps. Between 70 and 99 % of individuals had detectable anti-mumps antibodies using enzyme-linked immunosorbent assay (ELISA) or neutralization tests approximately ten years after initial vaccination. In two-dose recipients, mumps antibodies were detectable in 95 and 74 % of children 12 and 15 years after receipt of a second dose of MMR, respectively, but antibody levels declined with time.

In spite of numerous studies of the immunity to mumps infection, the protective level of antibodies in mumps remains unknown.

Contemporary epidemic features. Despite the fact that it was possible to reduce the incidence of mumps everywhere in the last two decades thanks to mass immunization, sporadic outbreaks of mumps began to occur globally (appendix 3). As with rubella, insufficient childhood vaccination coverage against mumps has led to an epidemiological shift in disease incidence to older age groups in which mumps complications are more prevalent.

During recent years, outbreaks of MuV infections have occurred in adolescent populations, many of whom had been vaccinated with mumps vaccines previously, in the USA, Canada, Australia, United Kingdom, and France. Several reasons were raised to explain the unexpected occurrence: waning immunity; the efficacy of mumps vaccine, which has varied according to the doses of vaccinations and different virus strain used for production of the mumps vaccine; a lack of asymptomatic natural boosting due to substantially reduced endemic disease, and how much the level of antibody persisted in body with time after vaccination or natural infection among population.

Pathogenesis

MuV is transmitted via the respiratory route by inhalation or oral contact with infected respiratory droplets or secretions. Primary viral replication occurs in the upper respiratory mucosal epithelium. Then, the virus drains to the local lymph nodes. MuV has a high affinity for T cells and efficiently replicates in these cells. Migrating mumps virus-infected T cells could facilitate spread from the respiratory tract to other sites of the body. MuV spreads to spleen and secondary lymphoid tissues. Viremia occurs, and then the virus spread to multiple secondary infection sites, including the salivary glands, inner ear, pancreas, heart, nervous system,

joints, kidneys, liver, gonads, and thyroid. The virus has only been sporadically detected in blood during infection.

Viral replication in the parotid gland results in perivascular and interstitial mononuclear cell infiltration, haemorrhage, oedema and necrosis of acinar and epithelial duct cells. MuV has been isolated from saliva 7 days before symptoms and up to 9 days after the appearance of parotitis. MuV has also been identified in the saliva of asymptomatic persons.

The mechanism behind the development of mumps parotitis and orchitis is unknown. It has been hypothesized that these complications result from lymphocytic infiltration and destruction of periductal cells that lead to blockage of the ducts in the salivary glands and the semeniferous tubules of the testes, respectively. Furthermore, the degree and duration of parotitis may be related to the amount of virus replication in the parotid gland and the development of a vigorous immune response. MuV has been recovered from semen and the testis, suggesting that epididymo-orchitis is the result of direct infection of testicular cells. However, an indirect immune-mediated mechanism has also been postulated. Both Leydig and germ cells are involved, associated with reduced levels of testosterone production. Necrosis of acinar and epithelial duct cells is evident in the germinal epithelium of the seminiferous tubules of the testes. Atrophy of the involved testicle occurs in approximately half of cases and can be associated with oligospermia and hypofertility, but rarely sterility.

Virus frequently disseminates to the kidneys. Viruria can be detected in the early phase of the disease. Epithelial cells of the distal tubules, calyces and ureters appear to be primary sites of virus replication. Kidney involvement in mumps is almost always benign, but cases of severe interstitial nephritis have been reported. In such cases, renal biopsy or postmortem necropsy show evidence of immune complex deposition, interstitial mononuclear cell infiltration and fibrosis, oedema and focal tubular epithelial cell damage.

MuV is highly neurotropic, with evidence of CNS involvement in up to half of all cases of infection, based on pleocytosis of the CSF. Symptomatic CNS infection is less common, but significant. MuV crosses the blood-brain barrier and accumulates in the subarachnoid space. The period of virus accumulation in the subarachnoid space can last from several days up to 4 weeks. It is believed that this is a period of secondary incubation and precisely this is the possible timing of the manifestation of meningitis from the onset of mumps infection. The excessive CSF volume both as a result of its overproduction and as a consequence of the entry into the subarachnoid space of a serous inflammatory infiltrate are leading in the pathogenesis of meningitis.

Little is known of the CNS pathology, since the disease is rarely fatal (in cases of encephalitis). Of the few postmortem cases examined, the pathology includes oedema and congestion throughout the brain with haemorrhage, lymphocytic peri-

vascular infiltration, perivascular gliosis and demyelination, with relative sparing of neurons. These latter observations suggest that in some cases of mumps encephalitis the inflammation stems from a para-infectious process.

Classification of mumps infection

The following clinical forms of mumps infection are distinguished:

1) typical;

2) atypical, which are presented by next forms:

– inapparent;

– subclinical;

Classification of mumps in ICD-11 for Mortality and Morbidity Statistics includes:

1D80 Mumps

1D80.0 Mumps without complication

1D80.1 Orchitis due to mumps virus

1D80.2 Meningitis due to mumps virus

1D80.3 Encephalitis due to mumps virus

1D80.4 Pancreatitis due to mumps virus

1D80.Y Other specified mumps:

– Mumps arthritis

– Mumps myocarditis

– Mumps nephritis

– Mumps polyneuropathy

– Mumps dacryoadenitis

– Mumps oophoritis

– Mumps hepatitis.

Clinical features

The typical forms of mumps are characterized by intoxication syndrome and damage of glandular tissue (salivary glands, pancreas, testes etc.) and / or CNS.

Depending on the severity of intoxication syndrome, local signs, and occurrence of complications, mild, moderate and severe mumps can be distin-guished in typical illness. The disease is mild or moderate in most cases. In mild course of illness the body temperature is subfebrile or increased up to 38,5 °C, there are mild symptoms of intoxication, salivary glands are slightly swollen. Moderate forms of mumps are characterized by febrile fever, pronounced intoxication syndrome, and affecting of various organs. Severe mumps is marked by high grade and prolonged fever (up to 40 °C and greater for a week and longer), full-blown intoxication syndrome (asthenization, marked weakness, sleep disturbance, anorexia).

Development of meningitis, meningoencephalitis, pancreatitis, and orchitic suggests about severe form of the disease.

The atypical forms of mumps. *The subclinical form* proceeds without enlargement of salivary glands with mild symptoms or may manifest as a respiratory tract infection.

The inapparent (asymptomatic) form is characterized by the absence of symptoms, clinical signs, and patient complaints, confirmed by increased titer of specific antibodies in paired sera.

Salivary gland damage

The incubation period of mumps is 11–21 days (range, 9 to 26 days). Usually it is 15–18 days.

The prodromal period lasts from several hours to several days. Mumps begins with non-specific symptoms such as malaise, tiredness, myalgia, headache and low-grade fever.

The fastigium period. Within 1–2 days of appearance of non-specific symptoms, unilateral or bilateral (in 70 % of cases) swelling of the parotid glands (in cheek and jaw area) develops with pain (fig. 7). Parotid gland pain is the most obligatory symptom of mumps, it increases with eating especially sour food. The damage of salivary glands is accompanied by a febrile fever and intoxication symptoms. Several pathognomonic signs have been described in mumps parotitis:

1. Tenderness just beyond the angle of the jaw on running the finger toward the angle under the mandible (Hatchcock's sign). This occurs before any swelling can be made out.

2. A reddish prominence at the orifice of Stensen's duct due to hyperaemia and oedema of the buccal mucosa (Tresilian's sign, synonym Mourson's sign), positive in 50–80 % of cases.

3. Painful Filatov's points on palpation: in front of the earlobe, in the region of the apex of the mastoid process and in the place of the mandibular notch.

Parotid gland swelling is at its maximum at 1–3 days and gradually decreases by 7 days. Approximately 75 % of all cases of symptomatic mumps in children are full-blown but without complications. The submandibular and sublingual glands can be involved simultaneously or after parotid gland swelling. Isolated submaxylitis or sublinguitis are rare.

Generally, the clinical manifestations appear to be mild in younger children and more severe in adolescents and adults. In some cases, new waves of fever and intoxication syndrome are observed, and each new wave is associated with the appearance of another implication.

We believe that, such clinical forms as meningitis / meningoencephalitis, pancreatitis, orchitis, and oophoritis are not the complications of mumps infection, and they should be considered the natural manifestations of the disease.

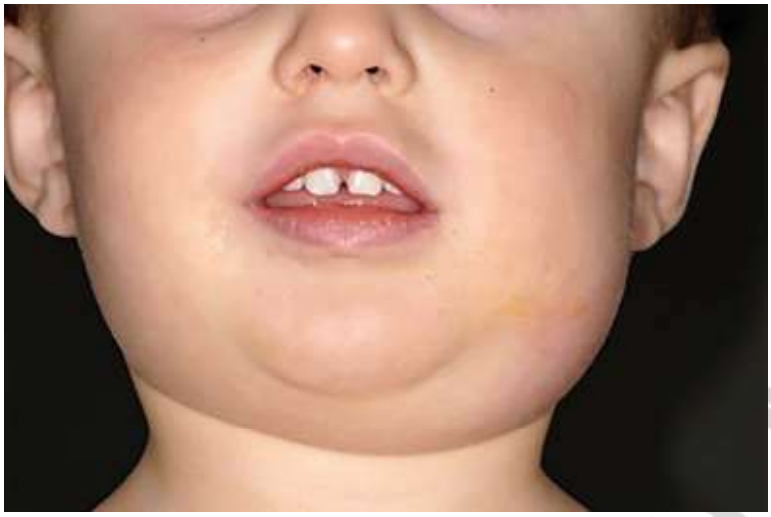

Fig. 7. Unilateral epidemic parotitis in a child

Central Nervous System damage

Mumps meningitis occurred in approximately 5–10 % of cases and encephalitis in < 0,5 %. Mumps meningoencephalitis is usually benign and death or major neurological complications are uncommon.

The CNS infection may be preceded, accompanied, or followed by involvement of salivary glands. A unique feature of mumps is the observation of pleocytosis, as evidence of inflammation of the CNS, unaccompanied by any clinical symptoms of meningitis or encephalitis. Meningoencephalitis may be the sole manifestation of mumps infection.

Meningitis. Most often mumps meningitis occurs in children aged 3 to 9 years. The majority of patients developed meningitis 3–8 days after the disease onset, but it can be occur later (up to 30 days). The disease is characterized by a fever, severe headache, mainly in the frontotemporal region, repeated or intractable vomiting, and lethargy. Meningeal signs appear on the first day of clinical course and are usually slight. Dissociation of the meningeal signs is often observed (in 60–70 % of cases): in the presence of clear neck stiffness (nuchal rigidity) and positive upper Brudzinsky's sign Kernig's and lower Brudzinsky's signs are negative or uncertain. The severity of the clinical course of meningitis depends on the magnitude of intracranial pressure. Lumbar puncture leads to a rapid improvement in the patient's well-being.

The acute phase of mumps meningitis lasts up to 5–7 days. The temperature is lytically reduced by 3–5 days of illness. Meningeal symptoms cease to be detected by 7–10 days, however, CSF normalization lags behind clinical recovery and is observed by 14 day or even later.

Lumbar puncture is of decisive importance in the diagnosis of meningitis. In the CSF a pleocytosis is detected up to 100–500 cells/mm3, predominantly lym-

phocytic but it can reach 20 000 cells/mm3. In the early days of the disease, CSF cytosis may be neutrophilic in some patients. The CSF protein level is normal or moderately elevated up to 0,6 g/L (60 mg/dL) in most patients, and the CSF glucose concentration may be decreased in 30 % of cases.

Meningoencephalitis is occurred rare, it may develop before or in the absence of parotitis, more often in preschool-aged children. The clinical manifestations of mumps meningoencephalitis are diverse, the following symptoms have been described: a high fever, severe headache, repeated vomiting, lethargy, drowsiness, impaired consciousness, delirium, irritability, restlessness, convulsions, paresis of cranial nerves and extremities, cerebral ataxia, psychosensory disorders. After 7–10 days of illness focal neurologic signs begin slowly fading away. The characteristic feature of mumps meningoencephalitis is a favorable course with complete recovery within 3–6 weeks of the disease.

Encephalitis as a sole manifestation of mumps appears very rare. It may begin in the absence of fever with depression of consciousness up to coma. In each case different combinations of clinical symptoms are possible. Encephalitis has the most severe course of illness; fatal outcomes have been described in children and adults in the pre-vaccination era.

Other mumps manifestations

Orchitis does not occur almost if the infection occurs prior to adolescence. This is the most common clinical manifestation after parotitis in adolescent boys and adult men, usually in those aged 15–29 years. In 80 % of all mumps orchitis cases, symptoms are first observed during the first 8 days of involvement of the salivary gland, usually unilateral involvement, with 15–30 % of cases showing bilateral involvement. Clinical findings include fever, malaise, vomiting, lower abdominal pain, and testicular pain. The testicle typically is swollen and tender for 3 to 7 days.

Mumps orchitis rarely leads to sterility but it may contribute to subfertility. It can also lead to oligospermia, azoospermia, and asthenospermia (defects in sperm movement). Unilateral disease can significantly, but only transiently, diminish the sperm count, mobility, and morphology. Impairment of fertility is estimated to occur in about 13 % of patients, while 30–87 % of patients with bilateral mumps orchitis experience infertility.

Oophoritis occurs in approximately 7 % of post-pubertal female patients. The illness is manifested by fever, lower abdominal and/or pelvic pain, and tenderness. The clinical symptoms last 5–7 days.

Outcomes of oophoritis are often favorable, however it may be the cause of infertility, early menopause, ovarian atrophy, menstrual irregularities, and juvenile uterine bleeding.

Pancreatitis occurs on the 4–6th day of mumps infection in 3 % of cases. The typical manifestations include upper abdomen pain and tenderness, fever, chills, nausea, vomiting, anorexia, and constipation.

Other rare manifestations are mastitis, dacryocystitis, thyroiditis, and myocarditis.

Complications

Complications of mumps are infrequent and less common after vaccination. Arthritis focused on the inflammation of one or more joints may occur as a complication of mumps. It is more frequently in males. Arthritis usually appears ten days after, but may antedate parotitis, and commonly lasts for two weeks, subsiding without residua. The small joints of the hands, wrists, knees, and ankles are most commonly affected.

Acute transverse myelitis is immune-mediated postinfectious process, characterized by abrupt onset of rapidly progressive weakness of the lower extremities accompanied by a loss of sensation and sphincter control. It may pro-ceed as a form of encephalomyelitis mostly develops in older children and young adults 7–15 days after parotitis.

Isolated cases of cranial nerve palsies including optic, facial, trigeminal and oculomotor nerves have been described. Neuritis of the facial and vestibulocochlear nerve are particularly characteristic for mumps. Symptomatic recovery and restoration of functions are observed within 1–2 months, except for cochlear neuritis. Deafness occurs in 0,5–5,0 / 100 000 cases of mumps, but mild degrees of hearing impairment are thought to be more common. Mumps-associated deafness may occur with or without meningoencephalitis after asymptomatic infection, and it is usually unilateral and often permanent.

Other rare complications include ascending polyradiculitis, thrombocytopenia, hepatitis, and nephritis.

Diagnosis

WHO established the definitions for mumps.

The clinical criteria for mumps is acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland, lasting two or more days and without other apparent cause.

The laboratory criteria for mumps is:

– Muv isolation or mumps viral RNA detection by PCR mumps;

OR

– IgM antibody detection or seroconversion or significant (at least fourfold) rise in serum mumps IgG titrer as determined by any standard serological assay.

Laboratory diagnostic methods for mumps

PCR. MuV can be isolated from throat swabs, urine and CSF. The samples should be taken in the first 2 days but not later than 7 days from the disease onset. However, the isolation of MuV is short-lived among vaccinated persons, and it is observed up to 2–3 days after disease onset.

Although **mumps viral culture** is rarely performed in uncomplicated cases the virus is readily isolated from CSF in cases of mumps meningitis.

Serologic testing. Investigation of blood should be carried out from 4 to 28th day from the disease onset to identify specific antibodies in mumps infection. EIA is used for detection of mumps antibodies. Recent infection may also be detected by measurement of low avidity IgG mumps antibodies.

CBC. Leukopenia, lymphocytosis, and normal level of ESR are revealed in mumps.

Biochemical analysis. Serum and urine amylase levels may be elevated as a result of inflammation and tissue damage in the parotid gland.

Differential diagnosis of mumps infection

The MuV is not the only cause of parotitis, there are other reasons non-infectious and infectious. Mumps should be differentiated from other diseases, which are accompanied a salivary gland swelling, fever, primary from viral and bacterial infections, as well as allergic and oncological diseases.

Many viral infections produce a parotitis with similar clinical features to mumps, including Epstein-Barr, cytomegalovirus, adenovirus, parainfluenza viruses type 1 and 3, coxsackie and influenza A viruses. The aetiology in each case should be confirmed by PSR test or serologically.

Acute suppurative parotitis may also appear similar to mumps parotitis. Acute suppurative parotitis is caused by a wide variety of pathogens, mostly by Staphylococcus aureus or Streptococcus spp., and is characterized by the sudden onset of unilateral induration and erythema that extends from the cheek to the angle of the jaw. The parotid gland becomes swollen and extremely tender. Purulent discharge may be expressed from the orifice of the parotid duct with gentle pressure. The infection can extend locally into surrounding tissue, the face, ear, or through the fascial plane to the mediastinum resulting in severe complications such as thrombophlebitis of the jugular vein (Lemierre syndrome) or septicemia. A febrile fever, marked intoxication, discoloration of the skin over the affected salivary gland in combination with a positive culture of drainage from the parotid duct, elevated WBC count with neutrocytosis and shift to the left will indicate this disease.

Cervical lymphadenopathy or lymphadenitis can be a common reason for seeking medical attention. Due to close localization of affected lymph nodes and salivary glands, these conditions may be misdiagnosed. A general impression of

the etiology of pathological process frequently can be made from a description of the course of illness and additional clinical signs. Ultrasound examination can help in challenging cases.

Other causes of damage to the salivary glands in children, such as salivary calculus, neoplasms, Mikulicz's disease, drug reaction are rare.

Mumps meningitis should be differentiated from the different types of meningitis, primarily aseptic. In the diagnosis it is necessary to take into account the epidemiological anamnesis, and clinical features of the disease. Thus,

enteroviral meningitis can be combined with herpangina, myalgia and characteristic exanthema. It is not impossible to suspect the aetiology based only on clinical findings in cases with isolated meningeal involvement in mumps, as well as in enterovirus infection. In all cases, the use of molecular-biological and immunological methods are required.

Management and treatment

Patients are recommended a plenty of fluid and a bed rest in the acute period of the disease, soft foods in a diet. Should be avoided acidic drinks such as fruit juice as these can irritate parotid glands. No specific therapy for mumps infection is available. Management is supportive and symptomatic. In severe cases a pathogenetic therapy with corticosteroids is used. Antibiotics are required only if there is secondary bacterial infection.

Dry heat is applied locally to the area of the salivary glands in parotitis. Compresses are contraindicated. Antipyretics such as acetaminophen and ibuprofen should be used in children with axillary temperature ≥ 38,5 °C (table). In cases of salivary gland pain may be used a short course of ibuprofen.

Antipyretics

Age	**Dosage of antipyretics**	
	Acetaminophen	**Ibuprofen**
Children over 1 months and < 12 years	10 to 15 mg/kg 3 to 4 times daily, repeated dose of 10 mg/kg should be given not earlier than in 4 hours, 15 mg/kg – in 6 hours, max. 60 mg/kg daily PO	For children over 3 months 5 to 10 mg/kg 3 to 4 times daily (max. 30 mg/kg daily) PO
Children 12 years and over and adults	500 mg to 1 g 3 to 4 times daily (max.3- 4 g daily)	200 to 400 mg 3 to 4 times daily (max. 1200 mg daily) PO

Patients with mumps arthritis are indicated to administer non-steroidal anti-inflammatory drugs (ibuprofen) for 5 to 7 days.

In the management of mumps orchitis a significant importance are bed rest, a suspensory bandage (for elevating scrotum) and non-steroidal anti-inflammatory

drugs for analgesia. Steroid administration helps in diminishing pain and oedema. For this purpose, prednisolone is used in a dose of 1–2 mg/kg/day in 3 divided doses orally, duration 7–10 days.

In cases of mumps encephalitis or polyneuropathies dexamethasone is included in the treatment at a dose of 0,5–1 mg/kg/day in 4 divided doses for 3–5 days IV, followed by a gradual withdrawal.

In most cases, the patients with mumps can be treated in outpatient departments. Children with complications and/ or severe clinical manifestations must be hospitalized. Hospitalization is also indicated for children from enclosed settings, persons living in dormitories or in dysfunctional families.

Discharge patients with mumps from a hospital are carried out after clinical recovery but not earlier than 5–9 days from disease onset (depending on the country).

Prevention

Mumps is a statutory notifiable disease. Notifications should be made on the basis of clinical suspicion. All cases should be reported within 24 hours – 5 days (depending on the country) to the local public health agency.

The specific prevention of mumps is vaccination. Mumps vaccine was introduced nationwide in 162 (from 194) countries by the end of 2017, and global coverage was estimated at 52 %. Mathematical models indicate that 85–90 % immunisation coverage is required to achieve herd immunity and the elimination of mumps transmission.

The mumps vaccine is a live attenuated strain, and a single dose gives more than 95 % long-lasting immunity, which is similar to that induced by natural infection.

Mumps vaccines are available either in monovalent formulation (vaccine directed at only one pathogen) or more commonly in combinations with other vaccines such as with vaccines against measles (MR), measles, mumps and rubella (MMR), or measles, mumps, rubella and varicella (MMRV). In most countries are recommended children get two doses of MMR vaccine, starting with the first dose at 12 through 15 months of age, and the second dose at 4 through 6 years of age.

In response to numerous mumps outbreaks reported throughout the United States in 2016 and 2017 (12 475 cases), the Advisory Committee on Immunization Practices (ACIP) recommended a third dose of MMR vaccine for groups of persons determined by public health authorities to be at increased risk for acquiring mumps because of an outbreak. Persons at increased risk for acquiring mumps are those who are more likely to have prolonged or intense exposure to droplets or saliva from a person infected with mumps, such as through close contact or sharing of drinks or utensils. During an outbreak, persons identified as being at increased

risk and who have received ≤ 2 doses of mumps virus–containing vaccine or have unknown vaccination status should receive one dose.

Vaccine efficacy and safety are dependent on the vaccine strain. Adverse reactions following vaccination are generally mild. They may include pain and redness at the injection site, low-grade fever, swollen glands and muscle aches.

To prevent the spread of mumps at the site of infection during the first 72 hours after contact of the index patient **emergency immunization** of contact persons (unvaccinated or who have not received two doses of MMR vaccine) should be recommended provided no contraindications exist. Immunoglobulin is not effective in preventing mumps.

The vaccine should not be given to:

– those who are immunosuppressed;

– those who have had a confirmed anaphylactic reaction to a previous dose of a measles-, mumps- or rubella-containing vaccine;

– those who have had a confirmed anaphylactic reaction to neomycin or gelatin;

– pregnant women.

The nonspecific prevention of mumps at the site of infection includes:

1. Isolation of patient for up to 9 days after symptom onset (at least up to 5 days in the USA, the UK). During this period exclusion cases from school, childcare or workplace is needed. Parents should be encouraged to keep their child away from other children and susceptible adults for the period of exclusion. Return convalescents of mumps to organized groups is allowed after clinical recovery but not earlier than the end of their isolation period.

2. Concurrent disinfection of articles soiled with nose and throat secretions.

SELF-CONTROL TASK

1. Name the causative agent of pertussis:

a) Haemophilus;
b) Bordetella pertussis;
c) Listeria monocytogenes;
d) Borrelia burgdorferi;
e) Bartonella henselae.

2. Index of contagiousness in pertussis is:

a) 5–10 %;
b) 20–30 %;
c) 40–50 %;
d) 70–90 %;
e) 100 %.

3. Name the key virulence factor (s) of pertussis pathogen:

a) filamentous hemagglutinin;
b) tracheal cytotoxin;
c) pertussis toxin;
d) pertactin;
e) adenylate cyclase toxin.

4. Describe the clinical manifestation (s) in the catarrhal stage of pertusis:

a) fever;
b) hoarseness, barking cough;
c) non-productive cough;
d) paroxysmal cough with inspiratory whoops.

5. Describe the clinical manifestation (s) in the paroxysmal stage of pertussis:

a) absence of fever;
b) post-tussive vomiting;
c) coughing fits occur more often at night;
d) paroxysmal cough with inspiratory whoops.

6. Which antibiotic should be prescribed in pertussis:

a) amoxicillin;
b) amikacin;
c) cefuroxime;
d) clarithromycin;
e) rifampicin.

7. Name the starting point of pertussis vaccination:

a) 2 months;
b) 3 months;
c) 16 months;
d) 12 months.

8. The causative agent of mumps infection belongs to:

a) orthomyxoviruses;
b) paramyxoviruses;
c) togaviruses;
d) caliciviruses.

9. The possible mode (s) of transmission of mumps virus is (are):

a) air-droplet;
b) contact;
c) common vehicle;
d) by insects.

10. Describe the duration of incubation period in mumps infection:

a) 1–3 days;
b) 2–7 days;

c) 7–14 days;
d) 11–25 day.

11. Which of the following occurs in typical mumps cases:

a) cough;
b) rash;
c) a sore throat;
d) adenoiditis;
e) salivary gland swelling.

12. CBC in mumps infection reveals:

a) normal or decreased leucocytes with predominating neutrophils;
b) normal or decreased leucocytes with predominating lymphocytes;
c) elevated leucocytes with predominating neutrophils, shift to the left;
d) atypical lymphocytes.

13. Which of the following would you recommend in mumps for children with moderate illness:

a) amoxicillin;
b) clarithromycin;
c) ibuprofen;
d) antihistamines;
e) immune globulin.

14. Preventive measures of mumps at the site of infection include:

a) isolation of patients;
b) terminal disinfection;
c) administration of human normal immunoglobulin to close contacts;
d) emergency immunization for susceptible individuals.

Answer key: 1 — b; 2 — d; 3 — a, b, c, d, e; 4 — c; 5 — a, b, c, d; 6 — d; 7 — a; 8 — b; 9 — a, b; 10 — d; 11 — e; 12 — b; 13 — c; 14 — a, d.

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Appendix 1

RECOMMENDED ANTIMICROBIAL TREATMENT AND POSTEXPOSURE PROPHYLAXIS FOR PERTUSSIS, BY AGE GROUP

Age group	Primary agents			Alternate agents
	Azithromycin	**Erythromycin**	**Clarithromycin**	**TMP/SMX***
Infants younger than 1 month	10 mg per kg per day in a single dose for 5 days (only limited safety data available)	Not preferred (associated with infantile hypertrophic pyloric stenosis). Use if azithromycin is unavailable; 40 to 50 mg per kg per day in four divided doses for 14 days	Not recommended (safety data unavailable)	Contraindicated in infants younger than two months (risk for kernicterus)
Infants 1 to 5 months of age	10 mg per kg per day in a single dose for 5 days	40 to 50 mg per kg per day in four divided doses for 14 days	15 mg per kg per day in two divided doses for 7 days	Contraindicated in infants younger than two months. For infants two months or older, TMP at a dosage of 8 mg per kg per day and SMX at a dosage of 40 mg per kg per day in two divided doses for 14 days
Infants (6 months or older) and older children	10 mg per kg in a single dose on day 1, then 5 mg per kg per day (maximum: 500 mg) on days 2 through 5	40 to 50 mg per kg per day (maximum: 2 g per day) in four divided doses for 14 days	15 mg per kg per day (maximum: 1 g per day) in two divided doses for 7 days	TMP at a dosage of 8 mg per kg per day, SMX at a dosage of 40 mg per kg per day in two divided doses for 14 days
Adults	500 mg in a single dose on day 1, then 250 mg per day on days 2 through 5	2 g per day in four divided doses for 14 days	1 g per day in two divided doses for 7 days	TMP at a dosage of 320 mg per day, SMX at a dosage of 1 600 mg per day in two divided doses for 14 days

* TMP/SMX — trimethoprim/sulfamethoxazole. TMP/SMX can be used as an alternative agent to macrolides in patients two months and older who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of B. pertussis.

Appendix 2

CLASSIFICATION OF THE PARAMYXOVIRIDAE PATHOGENIC FOR HUMANS

Grade	**Name**			
Class	Monjiviricetes			
Order	Mononegavirales			
Family	Paramyxoviridae			
Subfamily	Paramyxovirinae			Pneumovirinae
Genus	Paramyxovirus	Morbillivirus	Rubulavirus	Pneumovirus
Species	– Human parainfluenza virus type 1 – Human parainfluenza virus type 3	Measles virus	– Mumps virus – Human parainfluenza virus type 2 – Human parainfluenza virus type 4a – Human parainfluenza virus type 4b	Human respiratory syncytial virus

Appendix 3

MUMPS REPORTED CASES ACCORDING TO THE WHO

WHO region	**Number of mumps reported cases**				
	2019	**2018**	**2017**	**2016**	**2015**
Africa	38 795	54 482	41 490	100 576	28 492
Americans	60 294	68 290	52 839	27 511	19 115
South-East Asia	3055	32 018	61 783	31 739	42 937
Europe	24 363	20 114	26 965	21 364	10 072
Eastern Mediterranean	9663	23 145	43 053	75 680	20 391
Eastern Mediterranean	33 629	303 978	334 654	335 304	264 774
Global	169 799	502 027	560 784	592 174	385 781

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