**Exanthemic infections**

**(pictures for this seminar are in the PowerPoint presentation)**

For the purpose of rapid differential diagnosis, it is practical to classify exanthems **according to the appearance and character of the efflorescence**

* **Maculopapular**
	+ Measles, rubella, 5th and 6th diseases, scarlet fever, toxic shock syndrome, APEC syndrome
* **Vesicular, vesiculopustular**
	+ Varicella, herpes zoster, Kaposi's varicella dermatitis, hand-foot-mouth disease, streptococcal and staphylococcal impetigo, erythema multiforme
* **Petechial or hemorrhagic**
	+ Invasive meningococcal disease, peripheral embolization in infective endocarditis
* **Other specific skin manifestations not classifiable in the previous categories**
	+ Erythema nodosum, Gianotti-Crosti syndrome

**Cave!**

Urgent skin findings (need for rapid diagnosis and therapeutic intervention)

* bleeding skin manifestations (meningococcemia, septic embolization in infective endocarditis)
* scarlatiniform exanthema with hypotension (toxic shock syndrome)

**Maculopapular exanthema**

 **Measles (morbilli)**

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| --- | --- | --- | --- | --- | --- | --- |
| **Etiology** | **Vaccination**  | **Prevalence in the Czech Republic**  | **Transmission** | **Incubation period** | **Infectiousness** | **Mandatory isolation** |
| Morbilivirus | mandatory | unique | by air, direct contact, droplets | 8-14 days  | high, four days before and 5 days after the appearance of the rash | Yes |

**Etiology and epidemiology of measles**

Measles is caused by an enveloped RNA virus of the genus *Morbillivirus,* subfamily *Paramyxoviridae. The* only source of the virus is the sick person, who is infectious to his/her surroundings as early as four days before seeding of the typical exanthem and for another six days after seeding. The virus is transmitted by airborne droplets, direct contact with nasal and nasopharyngeal secretions, and, rarely, indirectly by contaminated objects. The disease manifestation rate in susceptible contacts is almost 100%. The incubation period is between 10 and 12 days.

**Pathogenesis**

After entering the body, the virus multiplies on the mucous membranes of the upper respiratory tract and passes to the regional lymph nodes.

Specific antibodies begin to form at the time of exanthema seeding and provide long-term, probably lifelong immunity. However, cell-mediated immunity is crucial for suppression of primoinfection, and patients with T-lymphocyte deficiency may have a severe or fatal course or atypical manifestations. Paradoxically, the immune response against measles virus induces reduced immune defences against other pathogens, which may persist for several weeks after the acute manifestations of the disease have resolved. At that time, the patient is more susceptible to secondary bacterial and viral infections and may also reactivate previously latent infections.

**Clinical picture**

After the incubation period, the ***prodromal (catarrhal) stage of*** the disease manifests first. Its manifestations include

* fever up to 40°C
* fatigue, lack of appetite
* respiratory symptoms - catarrhal rhinitis, dry cough
* catarrhal conjunctivitis
* Koplik's spots - small white dots on the buccal mucosa, typically located opposite the second molars near Stenon's ducts, in severe cases elsewhere on the oral mucosa.

After about 4 days, the ***exanthem stage*** develops

* a conspicuous red maculopapular exanthema starting behind the ears and on the neck and gradually spreading to the face, trunk and extremities, also on the palms and soles of the hands
* especially on the face and torso, it starts to fade after 3-5 days, does not itch

Uncomplicated illness lasts 7-10 days, the longest usually persists cough.

**Complications**

Complications are described in almost 40% of patients. Measles virus damages the respiratory epithelium, which becomes less resistant to other agents. Both bacterial and viral superinfection can easily occur.

**Respiratory complications** include**:**

* otitis media and sinusitis, laryngotracheobronchitis
* secondary bronchopneumonia, caused mainly by *Streptococcus pneumoniae* and *Haemophilus influenzae*.
* primary interstitial pneumonia caused by direct exposure to the virus
* giant cell pneumonia without exanthema in immunocompromised persons

Severe course and consequences may result in **central nervous system involvement***.* It manifests as

* ***acute encephalitis* -** develops within two weeks after exanthem seeding and is an immunopathological reaction rather than direct damage by measles virus. It is usually accompanied by a recurrence of fever, headache, cerebellar symptoms or cranial nerve paresis, and severe cases by convulsions and impaired consciousness. The fatality rate varies between 3-5%. EEG changes, typical of encephalitis, are temporarily described in up to 50% of measles patients, even if they do not have typical encephalitic symptoms.
* ***measles inclusion encephalitis -*** occurs several months after infection in individuals with immature or deficient immune systems that cannot eliminate the virus from the CNS. It has been repeatedly described in transplanted children and HIV-positive patients. The prognosis is unfavourable, with neurological impairment gradually progressing to death.
* ***subacute sclerosing panencephalitis* - a** rare but lethal complication caused by reactivation of the virus persisting in the CNS. It occurs several years after acute illness and manifests as behavioural disturbances, convulsions, hypertonia to spastic paresis with subsequent death.

Measles is also complicated by appendicitis, diarrhea, hepatitis or keratoconjunctivitis, which can lead to vision loss in poorly nourished children with vitamin A deficiency.

**Diagnostics**

The most diagnostic procedure is a combination of direct and indirect evidence. Early in the disease (first 4 days of exanthema), detection of measles virus RNA by PCR is preferable. The material is nasopharyngeal/oropharyngeal secretion. For serological examination, blood sampling between days 4 and 28 after exanthem is relevant, when 90-100% of patients have positive IgM antibodies. This finding confirms acute infection. If only IgG antibodies are positive, paired serum should be tested to confirm infection and a significant rise in IgG should be demonstrated.

**Differential diagnosis**

In the differential diagnosis it is necessary to distinguish toxoallergic exanthema or exanthema caused by other viruses (enteroviruses, adenoviruses, rubella virus).

**Therapies**

A specific virostatic is not available, therapy is symptomatic. Antibiotics are indicated for bacterial complications. In this disease, mandatory isolation is ordered.

**Prevention and prophylaxis**

Measles vaccination is part of the compulsory vaccination calendar. Post-exposure immunization is possible, both active (by administering the vaccine within 3 days of contact with the patient) and passive (by administering normal human immunoglobulin within 6 days of contact).

 **Rubella (rubeola)**

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| **Etiology** | **Vaccinations**  | **Occurrence in the Czech Republic**  | **Transmission** | **Incubation period** | **Infectivity** | **Mandatory isolation** |
| Rubivirus | mandatory | Rare | direct contact, droplets,transplacental transmission to the fetus | 12-23 days | high, but lower than measles, 7 days before and 4 days after sowing of exanthem | No |

Rubella is considered a benign disease, clinical manifestations are mild and complications are rare. The exception is acute infection in pregnant women, when the virus passes easily transplacentally to the fetus. The consequence may be miscarriage or rubella embryopathy

**Etiology, epidemiology, pathogenesis**

The causative agent is rubivirus, an RNA virus of the *Togaviridae* family*.* Spread by direct contact and droplets, exanthema is an immune response to viral antigens.

**Clinical picture**

* prodromal stage - mild catarrhal symptoms (not always), painful swelling of the nuchal, submandibular or retroauricular lymph nodes, subfebrile (not necessarily)
* exanthem sowing - small-spotted, pink, not merging, starting on the face, spreading to the trunk, only hinted on the limbs. Enanthema on mucous membrane of palate.
* up to 50% of patients may be asymptomatic

Complications may include thrombocytopenia or arthralgia of small joints, and encephalitis is very rare.

**Congenital rubella**

*Rubella virus is the most dangerous human teratogen.* **Congenital****rubella** *syndrome (***CRS**) was first described in 1941, more than 20 years before the discovery of rubella virus. *Australian ophthalmologist Norman Gregg observed an increased incidence of cataracts in newborns born during the rubella epidemic, many of whom also had severe heart defects and nearly a fifth died shortly after birth. Thus, for the first time, the function of the placenta as an absolute barrier against infection was called into question.*

***Pathogenesis***

*In primoinfection of a pregnant woman (even asymptomatic), the virus spreads haematogenously and can cross the placental barrier. It induces necrosis of the chorionic epithelium and endothelial cells; necrotic cells in the fetal circulation cause microtrombi and ischemia of tissues and organs. The risk of fetal infection is highest until the 11th week of gestation, when it reaches up to 90%, after which it decreases. This is also the period of highest risk of congenital malformations, which occur in up to 80% of infected foetuses, with approximately 20% of foetuses miscarrying. If infection of the fetus occurs between 12 and 18 weeks of gestation, isolated hearing loss is a common consequence. The risk of fetal infection increases again after the 26th week, but the risk of malformations is virtually zero.*

***Clinical picture and consequences***

*The manifestations of* CRS can be permanent or transient, only seen in the perinatal period, or late. They are summarised in Table 2.

Table 2: *Clinical and laboratory manifestations of congenital rubella syndrome*

|  |  |  |
| --- | --- | --- |
| Permanent disability | Transient manifestations | Late effects |
| * *cataract, microphthalmos, glaucoma, retinopathy*
* *sensorineural deafness*
* *heart defects (patent ductus arteriosus, hypoplasia of the a. pulmonalis, right ventricular hypertrophy)*
* *microcephaly, psychomotor retardation*
 | * *low birth weight*
* *thrombocytopenia, haemolytic anaemia*
* *hepatosplenomegaly, icterus, extramedullary haematopoiesis*
* *meningoencephalitis*
 | * *thyreopathy*
* *growth hormone deficiency*
* *diabetes mellitus*
* *psychomotor retardation*
* *deafness*
* *rare progressive rubella panencephalitis-fetal*
 |

**Rubella diagnostics**

Specific antibodies are used; IgM positivity is indicative of an acute infection, which is positive as early as day 3 after the rash appears and persists for 4-12 weeks. IgG antibodies are formed on day 5-8 after the onset of the rash and persist for life. Viral RNA can be detected by PCR from nasopharyngeal fluid, preferably in the first three days after exanthema seeding.

**Therapies**

It is symptomatic, the patient needs to be isolated from susceptible persons, especially pregnant women. Causative virostatic is not available.

**Prevention**

The rubella vaccination is part of the compulsory vaccination schedule. The vaccine is given in two doses, from 13 to 18 months of age and between 5 and 6 years of age.

**Exanthema subitum (6th disease)**

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| **Etiology** | **Vaccinations**  | **Occurrence in the Czech Republic**  | **Transmission** | **Incubation period** | **Infectivity** | **Mandatory isolation** |
| Sixth herpesvirus (HHV 6) Seventh herpesvirus (HHV 7) | not | frequent | direct contact, droplets, saliva | 5-15 days | medium to low | No |

**Etiology, epidemiology, pathogenesis**

HHV 6 and 7 are T-lymphotropic viruses that usually spread from adults with asymptomatic reactivation to infants and toddlers. In adulthood, probably 60-90% of the human population is infected. Both HHV 6 and 7 persist in T-lymphocytes after primoinfection and often reactivate in immunocompromised patients. The clinical picture is different in immunocompetent and immunosuppressed patients.

**Clinical picture in immunocompetent persons**

The disease is most common between the ages of 9-21 months. In the first six months of life, the infant is protected by maternal antibodies, and primoinfections are rare.

Primoinfection usually occurs in two stages

* + ***Prodromal febrile stage*** - sudden rise in temperature up to 40°C. Temperatures usually last 3-4 days, up to 6 days in about 15% of children. Other clinical findings are poor, the general condition is usually not markedly altered. Febrile episodes may be accompanied by mild respiratory symptoms, including serous otitis or cervical lymphadenopathy.
	+ ***sowing of exanthema*** - after the temperature drops, a small speckled pink exanthema is sown first on the body, then on the neck and legs. It does not itch and may persist for several hours to two days. It is sometimes accompanied by oedema of the eyelids (Berliner's sign).

**Cave!**

* The febrile state sometimes leads to the non-indicated administration of antibiotics and the subsequent exanthema can then be misinterpreted as an allergic reaction to antibiotics or antipyretics.
* This usually benign disease can be complicated by febrile convulsions, and up to one third of cases of febrile convulsions in infants and toddlers are attributed to exanthema subitum.

**Diagnostics**

In exanthema subitum, the diagnosis is usually made on the basis of typical clinical manifestations. If uncertain, it can be confirmed by the detection of specific IgM antibodies in serum.

**Therapies**

Treatment of the 6th disease in children is symptomatic.

 **Erythema infectiosum (parvovirus, 5th disease)**

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| **Etiology** | **Vaccinations**  | **Occurrence in the Czech Republic**  | **Transmission** | **Incubation period** | **Infectiousness** | **Mandatory isolation** |
| Parvovirus B19 | not | frequent | droplets, close contact, from mother to fetus | 10-21 days | medium, at the time of exanthema seeding the patient is already non-infectious  | No  |

**Etiology, epidemiology, pathogenesis**

The disease is caused by human **parvovirus *B 19****, a* small DNA virus classified in the genus *Erythrovirus* due to its ability to replicate in erythrocytic blood cells*.* It is widespread worldwide, with primoinfection usually occurring in childhood, most commonly between the ages of 4 and 10 years. Approximately 50% of 15-year-old children have detectable antibodies. In the elderly, more than 80% are seropositive. The infection has a marked seasonal pattern, from late winter to early summer. Increased numbers of cases may be seen every three to four years, and school epidemics are common. The source of infection is an infected person with an inapparent or manifest course; infection is spread by droplets or close contact. Infectiousness is reported to be around 50% for persons living in close contact with the patient.

The gateway to infection is the airway epithelium. During subsequent viremia, the target cells of the virus are mainly erythrocyte precursors in the bone marrow.

**Clinical picture**

The disease may be asymptomatic, with clinical manifestations in about 20% of infected persons. It may begin with ***prodromal symptoms***, which include fever, headache, mild gastrointestinal symptoms. However, an afebrile course is more common, in which the first manifestation of the disease is ***exanthema.***

Exanthema is characterized by

* starts on the cheeks and around the nose, often absent around the mouth
* soon appears on the trunk and extensor surfaces of the limbs
* the large reddish-purple spots gradually merge and fade from the centre, giving them a sometimes bizarre garland-like shape
* it can persist for several weeks, when it temporarily disappears, but with higher blood circulation (bath, physical activity) it becomes more pronounced again.
*

**Complications**

***Arthralgia*** to ***arthritis*** is a common complication of the disease*.* They are reported by about 8% of children and most adult women. In children, the knee joints and ankles are most commonly affected, while in adults the small joints of the hands and feet are more likely to be affected. Clinically, it resembles rheumatoid arthritis, and even elevated levels of rheumatoid factor and antinuclear antibodies may be transiently detected, but there is no erosive destruction of the joint. The virus can be detected by PCR in synovial tissue. Arthritis usually lasts 1-3 weeks, but protracted courses of more than a year have been described. Parvovirus B 19 is also associated with another type of exanthema affecting the acral parts of the limbs, the **gloves and socks syndrome**.

**Clinical picture of acute parvovirus infection in specific patient groups**

Significant affinity for erythrocyte precursors in bone marrow→ destruction of these cells → transient decrease in red blood cell production.

Anemia is usually benign, however, for specific groups of patients it can be very severe

(see table)

Table 1

|  |  |  |
| --- | --- | --- |
| Hosted by | Clinical manifestations | Course and therapy |
| Patients with a red blood cell disorder(hereditary spherocytosis, thalassaemia, enzymopathy, autoimmune haemolytic anaemia, etc.) | Transient aplastic crisis* Anemia
* abdominal pain
* in severe cases shortness of breath, confusion, cerebrovascular complications
* decrease in haematocrit and reticulocytes in the blood count
* erythrocyte precursors virtually disappeared in the bone marrow
 | Acute* patients are highly infectious during aplastic crisis
* blood transfusions are indicated
* the adjustment of erythrocyte values occurs within 10 to 14 days.
 |
| Fetus and newbornSignificant risk mainly in the 10th-20th week of pregnancy | * severe anaemia, myocarditis
* fetal hydrops
* chronic aplastic anaemia in the 3rd trimester
 | acute or chronic* careful and repeated fetal monitoring for 10-12 weeks is necessary
* degree of fetal anaemia assessed by determining the maximum flow rate in the arteria cerebri media, with pathological values indicating intrauterine transfusions
 |
| Immunodeficient persons- insufficient antibody response → persistent viremia | * Selective inhibition of erythropoiesis in bone marrow → chronic anemia
* Typical exanthema is usually absent
 | Chronic* Administration of high doses of immunoglobulins is indicated
* The disease may recur
 |

**Diagnostics**

- usually based on the clinical picture.

- can be confirmed by the demonstration of specific antibodies. IgM antibodies start to form around day 10 and persist for 2-3 months. IgG antibodies appear after about two weeks and are detectable for life.

**Therapies**

Treatment of erythema infectiosum is symptomatic. In case of arthritis, non-steroidal antirheumatic drugs are recommended

 **Spála**

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| **Etiology** | **Vaccinations**  | **Occurrence in the Czech Republic**  | **Transmission** | **Incubation period** | **Infectiousness** | **Mandatory isolation** |
| *Streptococcus pyogenes* sc. A, rarely C and G | not | frequent | directly or by droplets, infected objects | 2-4 days | high, especially in collectives. After 2 days of ATB treatment, the patient is non-infectious | No |

**Epidemiology**

* spread by droplets or by direct or indirect contact,
* closed spaces and collectives
* most often children of preschool age, in adolescents and adults it is rare.

**Pathogenesis**

The nasopharynx is the gateway to infection, and rarely the wounded skin (morning sickness). Typical skin manifestations are mainly due to the action of streptococcal erythrogenic (newly pyrogenic) toxins. There are three known antigenic variants, and antibodies to only one of them are present in the body after the disease. Patients who have recurrent scarlet fever do not have a recurrence of the disease, but are infected with a streptococcus with a different toxin variant.

**Clinical picture**

The disease begins with fever, sore throat, and in younger children, abdominal pain and vomiting may initially dominate. Maculopapular pink speckled ***exanthema*** is characterized by:

* typical localization - lower abdomen, groin, inner thighs, gradual spread along the lateral side of the trunk to the axillae
* ***white dermographism*** (after pressure on the skin, a persistent rash appearance for up to 1 minute)
* rough to the touch, reminiscent of goosebumps (cutis carinata) or sandpaper

Other manifestations of the disease include an initial white coating on the tongue, which peels off from the tip from the second day onwards, until it becomes a deep red ***(raspberry) tongue*** with prominent papillae. The throat is reddened ***and*** the ***tonsils*** may be ***catarrhal*** to ***pseudomembranous. Circumoral discharge*** (Filatov's sign) can be observed around the mouth, in some children ***Shramek's sign*** - whitish papules around the nail bed - is also evident. After 2-3 weeks there is ***peeling of the skin*** on the acral parts of the limbs.

**Complications**

* ***acute*** (bacterial) - *peritonsillar* and *retropharyngeal abscess, otitis media*
* ***Late*** (sterile) - poststreptococcal *glomerulonephritis* (haematuria, proteinuria, oedema to renal insufficiency caused by deposition of immunocomplexes in the glomerular basement membrane) and *rheumatic fever* (endocarditis and myocarditis, less frequently also arthritis caused by cross-reaction of antibodies to M protein with human tissues - currently rare in Europe).

**Diagnostics**

- usually based on clinical picture + culture of tonsil swab.

- rapid detection of streptococcal antigen (StreptTest) is also possible, but it does not allow antibiotic susceptibility to be determined.

- signs of bacterial inflammation in lab tests (leukocytosis, neutrophilia, elevation of CRP)

**Therapies**

The basic ATB is **penicillin**, resistance of pyogenic streptococci to penicillin has not been described so far.

The goal of therapy of streptococcal infection is not only to manage the acute condition, but also to prevent acute and late complications (rheumatic fever, glomerulonephritis).

* parenteral form (procaine- benzylpenicillin intramuscularly once a day, at a dose of 25-50 MIU/kg, with a maximum of 1.5 MIU/day). The duration of treatment is 5 days, on the 6th day depot benzathine - benzyl penicillin is administered intramuscularly at the same daily dose with a maximum of 1.2 MIU/day.
* p.o. treatment- penicillin 7- 10 days.
* for penicillin allergy, macrolides or clindamycin are alternatives; *Streptococcus pyogenes* sensitivity should be checked,

the patient remains in isolation for the duration of the treatment, usually in a home environment, rest for 1 week and then 1 week of convalescence is recommended. At week 3, inflammatory parameters are checked, baseline urinalysis and clinical cardiac examination are performed.

 **Toxic shock syndrome**

Some strains of *Streptococcus pyogenes* and *Staphylococcus aureus* produce toxins that act as superantigens and are capable of inducing a marked systemic inflammatory response, resembling severe sepsis, with the development of shock and multi-organ failure. This condition is usually accompanied by typical cutaneous and mucosal manifestations.

The source of the staphylococcal toxin can be a common staphylococcal infection anywhere in the body (e.g. on the skin) or a menstrual tampon. Streptococcal toxic shock syndrome can accompany streptococcal invasive infections.

**Clinical picture**

Basic clinical manifestations

* fever
* muscle pain
* diarrhea, nausea, vomiting
* rapidly onset hypotension
* scarlatiniform exanthema, sometimes petechial, with white dermographism, mainly localised on the trunk and extensor surfaces of the extremities
* redness of mucous membranes (oropharynx, possibly vagina)
* renal and hepatic impairment, ARDS, coagulopathy
* sometimes confusion to impaired consciousness

**Cave!**

The disease may resemble a severe course of scarlet fever, but a warning sign is rapidly developing hypotension that is reluctant to respond to treatment with conventional crystalloids.

**Therapie**s

Monitoring of vital signs in the intensive care unit is essential, management of hypotension is essential, circulatory support with catecholamines and oxygen therapy is usually necessary. Antibiotics are administered intravenously, usually a combination of a betalactam antibiotic (crystalline penicillin G, oxacillin, cephalosporin I.gen.) and clindamycin or linezolid.

**Vesicular, vesiculopustular exanthema**

 **Chickenpox (varicella)**

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| **Etiology** | **Vaccinations**  | **Occurrence in the Czech Republic**  | **Transmission** | **Incubation period** | **Infectiousness** | **Mandatory isolation** |
| Varicella-zoster virus (VZV) | Recommended | High | by air, direct contact, droplets | 10-23 days | high, one day before sowing and 7 days after the appearance of the rash | No |

**Epidemiology and pathogenesis**

Primoinfection with varicella-zoster virus (VZV) occurs as generalized vesicular exanthema. The virus is highly infectious, the source is an acutely ill person, for 1 day before and 7 days after the finding of the first vesicle. During this period, isolation of the patient in the home environment is necessary, and if hospitalization is necessary, then in an isolation box in the infectious diseases ward. In immunosuppressed patients, the course of the disease may be prolonged and infectiousness may persist longer. A severe to fatal course has been described in otherwise healthy children treated with high doses of corticosteroids.

After primoinfection, the virus persists in the sensory ganglia of the cranial and spinal nerves for life.

**Clinical picture**

Exanthema is accompanied by increased temperature and fatigue. Initially macules to papules change in a few hours to first clear vesicles and later turbid pustules. The first efflorescence often forms in the scalp, then on the face, trunk and limbs. The development of efflorescences takes several days, and on the 7th-8th day of the disease all vesicles and pustules are usually already transformed into dry crusts. The exanthema is not painful but itches. On the mucous membranes of the oral cavity and genital area, the equivalents of cutaneous vesicles, small aphthous lesions may appear.

**Complications**

* ***bacterial superinfection of*** skin lesions ***(****impetiginization*), more rarely phlegmon to abscess of subcutaneous tissue and soft tissue
* ***central nervous system involvement*** - in children usually *cerebellitis* on immunopathological basis, benign, without permanent sequelae, in adults more severe *encephalitis*
* interstitial varicella ***pneumonia*** or secondary bacterial bronchopneumonia
* ***thrombocytopenia or*** immune thrombocytopenic purpura

**Diagnostics**

In most cases, a typical clinical picture is sufficient. If the skin findings are inconclusive, direct detection of the virus from uncured vesicles (PCR) or indirect detection (IgM antibody positivity in serum) can be used.

**Therapies**

In children, the course of varicella is usually uncomplicated, virostatics are not necessary, treatment is symptomatic (antipyretics, antihistamines, topical disinfectant solutions such as Betadine are currently preferred rather than the previously used liquid powder). Causal treatment with acyclovir is indicated:

* in adult and childhood diseases over 12 years of age, where there is a higher risk of complications
* in patients at risk (e.g. chronic skin or lung disease, pregnant women)
* for severe and complicated courses at any age
* in immunosuppressed patients

The recommended dosage and form of acyclovir is given in Table 2.

1. e.g. chronic skin or lung disease, pregnant woman, if the general condition does not require hospitalisation

**2.2**. **Shingles (Herpes zoster)**

**Pathogenesis**

After primoinfection, VZV persists for life in the sensory ganglia of the cranial and spinal nerves. During a transient or prolonged decline in the cellular immune response, the virus is capable of reactivation and spreads along the sensory nerves to the corresponding dermatome. Here it manifests itself as a localised seeding of vesicles - shingles. Such reactivation is rare in children.

**Clinical picture**

Vesicle seeding, which usually affects 1-3 dermatomes, may be preceded by several days of pain in the area. The development of densely seeded vesicles over the macula and papule is similar to that of varicella, as is the healing of the crust. The course is usually milder in childhood and the risk of developing postherpetic neuralgia (marked pain in the affected dermatomes even after healing of the skin eruptions) is low.

**Complications**

* involvement of the conjunctiva, cornea and deeper structures of the eye in herpes zoster seeding along the 1st branch of the n. trigeminus. Due to the risk of permanent visual impairment, local treatment is necessary in addition to general antiviral therapy.
* seeding of shingles on the auricle and around the ear is often complicated by peripheral paresis n.VII- Ramsay-Hunt syndrome
* in immunosuppressed patients the seeding may be generalized and resemble varicella
* bacterial superinfection of skin efflorescences
* postherpetic neuralgia
* aseptic neuroinfection

**Cave!**

Reactivation of the virus from sensitive ganglia can also occur without typical skin seeding (zoster sine herpete). The disease may present as aseptic meningitis or meningoencephalitis, where the virus can be detected by PCR in cerebrospinal fluid, or only as pain and increased skin tenderness in the affected dermatome.

**Diagnostics**

In case of diagnostic confusion, direct detection of the virus (PCR) can be performed from the contents of previously undried vesicles.

**Therapies**

Causal treatment with antivirals is indicated for each form of herpes zoster. Hospitalization and parenteral therapy is recommended when shingles is localized to the face, when CNS involvement is suspected, and in all immunocompromised persons.

 **Hand-foot-mouth disease**

**(Hand, foot and mouth disease, HFMD)**

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| **Etiology** | **Vaccinations**  | **Occurrence in the Czech Republic**  | **Transmission** | **Incubation period** | **Infectiousness** | **Mandatory isolation** |
| enteroviruses | not | smaller local epidemics in 5-6 year cycles | droplets, direct contact, contaminated objects | 3-6 days | high | No |

**Clinical picture**

It is manifested by the appearance of whitish blisters, which usually appear without prodromes on the mucous membranes of the lips, cheeks and hard palate, or even around the mouth. In about 75% of patients, papulovesicular exanthema occurs simultaneously on the soles of the feet, palms of the hands and sometimes on the extensor surfaces of the extremities, buttocks and genitalia. It may be itchy and painful. The vesicle contents are usually clear and heal spontaneously within 10 days. Initially, there may be febrile episodes lasting about 1-2 days.

**Diagnostics**

If the clinical picture is not conclusive, enterovirus can be detected in the vesicle contents by PCR. Testing for specific antibodies in serum is also possible, but usually requires paired sera.

**Therapies**

Treatment is symptomatic, includes rest, antipyretics, analgesics, sufficient fluid intake, and local or general antihistamines for itching exanthema. For the duration of the exanthem, the child should be excluded from the collective.

 **Impetigo**

(staphylococcal, streptococcal)

Impetigo most often affects young children, but it can also be secondary to other skin conditions ( e.g. impetiginization of varicella lesions or eczematous skin). It is a superficial skin infection and does not affect the deeper layers. It is highly infectious and easily transmitted by scratching and direct contact to other parts of the body and to other persons.

**Etiology and clinical picture**

The disease runs its course without fever and other general symptoms. Circumscriptions of affected skin may be up to several centimetres in size and may appear secondarily on other parts of the body. Most cases are streptococcal infections; staphylococcal impetigo is rarer (Table 3). When the etiologic agent is in doubt, culture of the blister contents is appropriate.

**Therapies**

In very young children or when larger areas of skin are affected, total ATB therapy against both potential pathogens is appropriate. In milder cases, topical ATB therapy (mupirocin, bacitracin) is sufficient. For streptococcal impetigo, the drug of choice is penicillin in the usual dose; if the etiology of impetigo is in doubt, a first-generation cephalosporin (cefadroxil) can be used

 **Erythema multiforme**, **Stevens-Johnson syndrome**

Exanthema appears on the skin in connection with a past or ongoing viral or bacterial infection; in children it is often related to *Mycoplasma pneumoniae* infection*.* However, it can also occur after the administration of certain drugs (barbiturates, sulphonamides, etc.). Circular, sharply demarcated macules appear on the trunk and limbs; in larger ones, a small papule, vesicle, or later crust is seen in the centre. The disease may also be accompanied by swelling and joint pain. **Stevens-Johnson syndrome** is a more severe form of erythema multiforme, in which both skin and mucous membranes are affected. Numerous vesicles form on the skin and the conjunctivae, lips, oral cavity, genitalia and anus are affected. The most severe form is **toxic epidermal necrolysis (Lyell's syndrome)**, where up to 30% of the body surface is affected.

**Petechial and hemorrhagic exanthemas**

 Hemorrhagic cutaneous manifestations are described as ***petechiae***, small hemorrhages caused by capillary rupture or as ***suffusion****,* hemorrhages larger than 3mm. Typically, they do not disappear or fade when the skin is compressed.

* **Infectious**
	+ meningococcal sepsis or meningitis
	+ sepsis of other aetiologies, gonococcal bacteraemia
	+ infective endocarditis
	+ rickettsiosis
	+ viral haemorrhagic fever
	+ dengue fever
* **Non-infectious**
	+ thrombocytopenic purpura
	+ anaphylactoid (Henoch-Schonlein) purpura
	+ medicinal purpura
	+ Vasculitis

 **Meningococcal sepsis** (see separate seminar)

Non-specific maculopapular exanthema may be evident on the skin at the onset of the disease, but the typical skin findings are rapidly forming petechiae, which may be discreet and easily missed at first. However, within a few hours they progress to the appearance of larger skin suffusions, and peripheral cyanosis may also be present. The disease always has general symptoms (fever, muscle and joint pain, cephalea, hypotension). Hospitalization in an intensive care bed is necessary.

 **Infective endocarditis with septic embolizations**

Skin embolization may be seen in patients with left heart valve involvement. On the skin, they have the character of small hemorrhages to larger suffusions. They can also be found under the nails, on the conjunctivae, or on mucous membranes.

Note: *Petechiae can also form in sepsis of other etiologies (e.g. G-rods). Similar skin findings can also be observed in patients with generalized gonococcal infection, but usually there are no general manifestations of sepsis and the course is less severe.*

**Other specific skin manifestations**

 **Erythema nodosum**

Nodular erythema is considered to be an immunopathological response (most likely type IV hypersensitivity reaction) induced by various noxious agents, including infectious ones. It is associated with recent salmonellosis, campylobacteriosis, yersiniosis, streptococcal infections, tuberculosis, but also with non-infectious diseases (sarcoidosis, idiopathic intestinal inflammation) or drugs. Solid, slightly painful nodules in the subcutaneous tissue, 2-4 cm in size, occur symmetrically over the extensor parts of the extremities, most often on the tibiae, sometimes on the forearms. The patient may be febrile at the onset of the disease, often reporting pain on walking. Diagnosis is most often clinical, and lung X-ray is performed to exclude TB and sarcoidosis. Antiphlogistic agents are used in therapy, and corticosteroids in case of extensive findings. If an infectious cause is confirmed, it is treated with appropriate antibiotics.

**Kawasaki disease**

This rare systemic inflammatory disease mainly affects children under 5 years of age. The aetiology is not completely clear; currently the preferred theory is an immunopathologically activated inflammatory response in genetically predisposed individuals. Fever lasting more than 5 days is typical for the onset of the disease, other diagnostic criteria include:

* mucosal involvement (raspberry tongue, red lips, enanthema of the oral mucosa)
* bilateral non-purulent conjunctivitis
* maculopapular exanthema
* oedema and erythema of the acral parts of the limbs, in the subacute phase peeling of the skin
* cervical lymphadenopathy, uni and bilateral

Less common manifestations may include arthralgia and arthritis, abdominal pain, vomiting, pleural effusions. Coronary arteritis with aneurysm formation, which can cause myocardial ischaemia, myocarditis and pericarditis are serious complications. Laboratory investigations tend to show leukocytosis, mild anaemia, thrombocytosis, increased erythrocyte sedimentation rate, elevation of CRP and hepatic aminotransferases. Echocardiographic examination is essential. The drugs of choice are high-dose intravenous immunoglobulins (usually 2 g/kg once) and acetylsalicylic acid (30-50 mg/kg/day).

**Paediatric inflammatory multisystem response syndrome temporally associated with SARS-CoV-2 (PIMS-TS)**

The disease manifests itself 2-6 weeks after exposure to the new SARS-CoV-2 coronavirus. Basic diagnostic criteria include age 0-19 years and febrile illness lasting more than 3 days and at least two of the following:

* bilateral non-purulent conjunctivitis
* exanthema including acral parts of the limbs
* redness of the lips and mucous membranes of the oral cavity
* diarrhea, vomiting abdominal pain
* hypotension, shock
* myocardial dysfunction, pericarditis
* elevation of inflammatory parameters
* troponin/NT-proBNP elevation
* Coagulopathy

The clinical picture may also include renal insufficiency, cephalea, meningismus, convulsions, cough, tachydyspnoe. Intravenous immunoglobulins and corticosteroids, as well as low-molecular-weight heparin and acetylsalicylic acid, are essential components of treatment.