DIFFERENTIAL DIAGNOSIS OF INFECTIOUS EXANTHEMS IN CHILDREN

Minsk BSMU 2023

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ДИФФЕРЕНЦИАЛЬНАЯ ДИАГНОСТИКА ИНФЕКЦИОННЫХ ЭКЗАНТЕМ У ДЕТЕЙ

DIFFERENTIAL DIAGNOSIS OF INFECTIOUS EXANTHEMS IN CHILDREN

Учебно-методическое пособие

Минск БГМУ 2023

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Отражены вопросы дифференциальной диагностики инфекционных заболеваний у детей, проявлющихся развитием сыпи.

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

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ABBREVIATIONS

CBC — complete blood count
CMV — Cytomegalovirus
CRS — Congenital Rubella Syndrome
DRESS — Drug Reaction with Eosinophilia and Systemic Symptoms
e.g. — exempli gratia (from Latin) that means for example
etc. — et cetera
EBV — Epstein-Barr virus
EN — Erythema Nodosum
ESR — erythrocyte sedimentation rate
HIV — Human Immunodeficiency virus
HFMD — Hand, Foot, and Mouth disease
HFRS — Haemorrhagic Fever with Renal Syndrome
HHV-6 — Human Herpes virus 6
HHV-7 — Human Herpes virus 7
HSV — Herpes Simplex virus
i.e. — id est (from Latin) that is to say
MD — Meningococcal disease
MIRM — Mycoplasma pneumoniae-Induced Rash and Mucositis
NSAIDs — Nonsteroidal anti-inflammatory drugs
PPGSS — Papular-Purpuric Gloves and Socks Syndrome
RMSF — Rocky Mountain Spotted Fever
SJS — Stevens-Johnson Syndrome
SSSS — Staphylococcal Scalded Skin Syndrome
TEN — Toxic Epidermal Necrolysis
TSS — Toxic Shock Syndrome
VHF — Viral Haemorrhagic Fever
VZV — Varicella Zoster virus

MOTIVATIONAL CHARACTERISTICS OF TOPIC

Total in-class hours — 7.

Childhood exanthem is one of the most common clinical issues, encountered by paediatricians in the hospital and the office. The vast majority of exanthems have a viral aetiology. However, skin rashes in children can be due to infectious reasons, such as bacteria, fungies, protozoa, helminths and non-infectious origin. The diagnosis is usually made on clinical grounds. The correct assessment of skin lesions along with other clinical and laboratory features of a particular disease, allows not only making a diagnosis properly, but also saves the patient's life in some cases (e.g., meningococcal disease, toxic epidermal necrolysis). The rapid accurate diagnosis is no less important for providing anti-epidemic measures in infectious diseases (especially highly communicable).

Despite the experience gained in the detection of exanthems in children, there are still diagnostic challenges to clinicians. In this regard, relevant questions remain for diagnosis and differential diagnosis of infectious diseases accompanied by exanthems.

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

Class tasks. *The students should know:*

– aetiology, epidemiology, pathogenesis of the most common infectious diseases in children and adolescents accompanied by exanthems (scarlet fever, measles, rubella, chicken pox, herpes virus infections, enterovirus infection, human parvovirus infection, yersiniosis, pseudotuberculosis, meningococcemia, etc.);

– the clinical signs and syndromes of the infectious diseases with rashes;

– the features of clinical course of the infections with exanthems in young children, vaccinated persons;

– the differential diagnosis of infectious diseases accompanied by exanthems in the different periods of the disease;

– clinical symptoms and special characteristics of emergency conditions in children with exanthems, the diagnosis and administering immediate care in life-threatening conditions;

– the indications for hospitalization of children with the diseases accompanied by exanthems;

– the major diagnostic methods of the infectious diseases accompanied by exanthems;

– the major complications and outcomes of the infectious diseases accompanied by exanthems;

– the principles of treatment of these diseases in children;

– prevention of infectious diseases with exanthems in children;

– anti-epidemic measures at the outbreak site;

The students should be able to:

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

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

– fill in medical documents in case of infectious disease accompanied by exanthem;

– organize preventive measures at the outbreak site.

The students should master:

– methods of epidemiological analysis of development of infectious disease accompanied by exanthem;

– methods of identifying the clinical symptoms, atypical, severe and complicated forms of infectious disease accompanied by exanthem;

– contemporary methods of clinical, instrumental and laboratory examination;

– methods of inpatient and outpatient giving first medical aid in life-threatening conditions;

– methods and forms of health education of the population.

Requirements for the initial level of knowledge. Revise:

– Human Anatomy: anatomical and morphological structure of the skin;

– Microbiology, Virology, Immunology: mechanisms of the development of immune response in the different infectious diseases accompanied by exanthems;

– Pathologic Anatomy: general patterns and mechanisms of development of pathological processes in the skin and mucous membranes;

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

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

– Paediatrics: differential diagnosis of clinical manifestations of infectious and non-infectious diseases in children;

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

Questions for self-control from related disciplines:

1. What pathogens cause the infectious diseases accompanied by exanthems in children? Give the characteristic of pathogens.

2. What primary and secondary skin lesions do you know? Give their description.

3. What are the methods of laboratory diagnosis of infectious diseases?

4. Name the pathomorphological changes in the skin and mucous membranes in infectious exanthems.

Test questions on the topic of the lesson:

1. What significant points should be clarified during patient's history taking in case of exanthem syndrome?
2. How examine the patient with rash?
3. What investigations have to be done to establish the disease aetiology in patients with rash and fever?
4. Describe clinical manifestations of the infectious diseases, accompanied by exanthems, and their clinical features.
5. Differential diagnosis of the infectious diseases accompanied by exanthems in the different periods of the disease.
6. Differential diagnosis of macular and maculopapular exanthems.
7. Differential diagnosis of vesicular and pustular exanthems.
8. Differential diagnosis of haemorrhagic exanthems.
9. Differential diagnosis of infectious and non-infectious exanthems.

INTRODUCTION

There are many common skin disorders requiring the clinical care of health-care professionals.

Skin rashes are among the commonest clinical presentations in childhood. Exanthem (i.e., exanthema) is another name for a rash or skin eruption. Enanthem (i.e., enanthema) is eruption on the mucous membranes of the oral cavity.

In some situations, infectious exanthem may be difficult to differentiate clinically from non-infectious disease. Common non-infectious causes include allergies (food allergy, drug reactions, atopic dermatitis, etc.), autoimmune disorders (e.g., systemic lupus erythematosus, Sjogren's syndrome, dermatomyositis, autoimmune hives, Kawasaki disease, multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19), local irritants (e.g., poisoning plants, diaper rash, heat rash), hereditary diseases, and insects bites.

The differential diagnoses of infectious rashes are extensive, ranging from self-limiting conditions (e.g., roseola) to life-threatening illnesses such as meningococcal disease. Common non-life-threatening diagnoses and "can't miss" life-threatening diagnoses are indicated in Appendix 1.

Exanthem may be the first indication of a potentially serious multi-organ disease or sepsis, and should be carefully evaluated. Generally, rash in the absence of fever or systemic symptoms is not urgent.

Rash may be categorized as maculopapular, petechial/ purpuric, vesicular/ bullous and scaly in nature. In many aetiologies these forms may coexist or evolve from one form to another (table 1).

Table 1

Aetiology of different types of rash in children

Type of rash	Viral aetiology	Bacterial aetiology	Other infectious reasons	Other reasons
Maculo-papular	Measles Rubella EBV Erythema infectiosum (parvovirus B19) Roseola infantum (HHV-6, HHV-7) Enterovirus Adenovirus Gianotti–Crosti syndrome Unilateral laterothoracic exanthema HIV (acute) West Nile virus	Staphylococcal and streptococcal toxic shock Scarlet fever Syphilis Mycoplasma infection Psittacosis Leptospirosis Borreliosis Typhoid fever Brucellosis Rickettsiosis Ehrlichiosis Arcano-bacterium haemolyticum	Toxoplasmosis	Kawasaki disease Pityriasis rosea Juvenile chronic arthritis Drug reaction DRESS syndrome Eczema Systemic lupus erythematosus Dermatitis
Petechial/ purpuric	Enterovirus EBV Papular purpuric gloves and socks syndrome Viral haemorrhagic fevers Congenital CMV/ rubella	Meningococcal disease Pneumococcal disease Leptospirosis Rickettsiosis	Malaria Leishmaniasis	Henoch–Schönlein purpura Haemolytic uremic syndrome Idiopathic thrombocyto-penic purpura Leukaemia Neuroblastoma
Vesicular/ bullous	Varicella Herpes simplex Monkeypox Enterovirus infection	Staphylococcal scalded skin syndrome Staphylococcal and streptococcal impetigo Mycoplasma pneumoniae infection Congenital syphilis	Dermatophyte infections	Stevens–Johnson syndrome Epidermolysis bullosa Miliaria Mastocytosis Metabolic causes Thermal burns Frostbite Bullous arthropod bite reactions
Scaly			Fungal, e.g. tinea	Eczema Psoriasis

DEFINITIONS OF RASH ELEMENTS

Macule — a flat area of color change < 1 cm in size (e.g., viral exanthem such as measles, rubella, and morbilliform drug eruption).

Patch — a large macule > 1 cm in size (e.g., viral exanthem such as measles, rubella, and morbilliform drug eruption).

Erythema — a redness of the skin > 2 cm in size.

Papule — a raised area < 1 cm in size (e.g., wart).

Nodule — a larger papule > 1 cm in size (e.g., nodular prurigo).

Plaque — a flat-topped raised area (a cross between a nodule and a patch; e.g., psoriasis).

Vesicle — a small fluid-filled lesion (blister) < 0.5 cm in size (e.g., varicella, eczema herpeticum).

Bulla — a larger vesicle > 0.5 cm (e.g., bullous impetigo).

Pustule — a pus-filled lesion (e.g., folliculitis).

Wheal — a transient raised papule or plaque caused by dermal edema (e.g., urticaria).

Scale — flakes of stratum corneum (e.g., eczema, psoriasis).

Crust — dried serum, blood, or purulent exudate on the skin surface (e.g., impetigo).

Erosion — loss of epidermis, heals without scarring (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis).

Ulcer — loss of epidermis and dermis, heals with scarring (e.g., venous ulcer, pyoderma gangrenosum).

Excoriation — loss of epidermis following trauma such as scratching (e.g., as can be seen in eczema).

Fissure — a split in the skin (e.g., angular cheilitis, palmoplantar keratoderma).

Lichenification — thickening of the skin with accentuation of skin markings (e.g., chronic eczema, lichen simplex chronicus).

Petechia — a pinpoint purpuric lesion (e.g., vasculitis, disseminated intravascular coagulation).

Purpura — an area of color change (red or purple) < 1 cm in size due to bleeding into the skin; does not blanch on pressure (e.g., vasculitis, disseminated intravascular coagulation).

Ecchymosis — a larger area of purpura (e.g., vasculitis, disseminated intravascular coagulation).

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

The causes of rash in childhood are frequently difficult to differentiate from each other. However, the incidence of many infections is more common for specific age groups, and the aetiology can be narrowed down by careful history and examination.

Significant points in patient's history

Prodromal symptoms. Most infectious rashes in childhood are associated with systemic symptoms, such as fever, catarrhal syndrome, gastrointestinal syndrome, lymphadenopathy. These symptoms may precede the onset of rash (appendix 2).

Associated symptoms. *Itching* common for chickenpox, herpes simplex infection, allergic contact dermatitis, insects bites.

Respiratory symptoms may be associated with roseola infantum and more severely with pneumonitis in measles, chickenpox, and psittacosis.

Gastrointestinal symptoms may be a feature of measles, roseola infantum, toxic shock syndrome, typhoid and leptospirosis.

Hepatitis may occur in roseola infantum, Gianotti–Crosti syndrome, and leptospirosis.

There may be coexisting meningitis in meningococcal sepsis, enterovirus infection, and leptospirosis, or rarely an encephalitic picture with measles, rubella, chickenpox, erythema infectiosum, and roseola infantum.

Joint symptoms may be associated with rubella, erythema infectiosum, yersinia infection, psittacosis, brucellosis, and at a late stage in Lyme borreliosis.

Evolution of the rash. Some rashes appear as generalized lesions over the entire body at onset, while others change in nature or distribution (table 1).

Several rashes desquamate with time, including measles, scarlet fever, yersinia infection, Kawasaki disease, syphilis, and various toxin-mediated infections.

Exposure to infections. Contact with other people with similar symptoms is important, as some diseases are highly infectious (e.g., chickenpox, erythema infectiosum).

Exposure to insects that might transmit infections is relevant (e.g., in Lyme disease — deer ticks and dengue fever — mosquitoes).

Contact with animals that might transmit infections is relevant (e.g., in leptospirosis – rats, toxoplasmosis – puppies and kittens, psittacosis – birds).

Ingestion of potentially infected foods is relevant (e.g., in toxoplasmosis — soft cheeses and pâté, brucellosis — unpasteurized milk).

Foreign travel. With increasing worldwide travel, imported infections are an important cause of rashes. Typhoid and paratyphoid fever are common infections in febrile children who have returned from travelling (Sub-Saharan Africa, India and South-East Asia), which may present with rose spots on the abdomen in older children. Dengue fever is the most commonly identified cause of maculopapular rash in endemic areas (Americas, Africa, the Middle East, Asia, and the Pacific Islands). In certain circumstances, it can also present with a haemorrhagic rash. Malaria is a common infection and a rare cause of purpuric rash. Countries other than tropical countries are also the source of infections, e.g. Rocky Mountain spotted fever and West Nile virus in the US and leishmaniasis in Southern Europe.

Time of year. Many infections are seasonal, so awareness of prevailing microorganisms is important. Enterovirus infections (echovirus, coxsackievirus, and enterovirus) occur predominantly in the summer months. Erythema infectiosum tends to occur in late winter and early spring. Tropical infections also have seasons of increased incidence (e.g., dengue fever and malaria).

Immunization history. High risk of infection in unvaccinated persons and atypical clinical presentation in vaccinated.

Drug history. Drugs may cause rash, even without a concomitant infection, and may be due to an allergy or a side effect. Drugs with rash as a well-recognized side effect include anti-epileptics, antibiotics, and antimalarials.

The administration of amoxicillin during EBV infection has traditionally been considered to cause a widespread rash, although the strength of this association has recently been questioned.

Sun exposure may exacerbate rashes caused by drugs or parvovirus B19.

Drugs may cause different types of rash (e.g., maculopapular, urticarial, erythema multiforme, and SJS).

Evolution and disappearing of the rash under antihistamines or corticosteroids matters in diagnosis.

The physical examination

Nature of the rash. The key to diagnosis is the nature of the rash — maculopapular, petechial/purpuric, vesicular/bullous, or scaly (table 1).

Some agents cause several different types of rash (e.g., enteroviruses, which can cause maculopapular, petechial, and vesicular rashes).

In chickenpox, different stages of the rash can occur at the same time — maculopapular, vesicular, and crusted. Historically, this differentiated it from smallpox where all the vesicles had similar morphology.

Some rashes have classical morphology, e.g. the rash of TSS, which is described as looking like sunburn, the bullseye lesions in Lyme disease, the sandpa-

per rash of scarlet fever, and the salmon pink macules in juvenile chronic arthritis. However, a lack of classical features does not necessarily preclude the diagnosis.

Rash distribution also differentiates between pathogens. It may change with time, so the history of its evolution and re-examination are important.

Centripetal rashes predominate or start on the extremities and include HFMD, syphilis, RMSF, dengue fever, and smallpox.

Centrifugal rashes predominate or start on the trunk and include measles, rubella, chickenpox, and scarlet fever.

Changes in the mucous membranes. Several skin rashes have associated oral lesions that can easily be missed if the buccal cavity is not specifically examined. A strawberry-red tongue may be the first sign of scarlet fever or, in a child, a sign of Kawasaki disease or MIS-C. Mucosal changes can occur in patients with scarlet fever, Kawasaki disease, TSS, and drug reactions, including SJS. Conjunctivitis may occur in measles, rubella, adenovirus infection, scarlet fever, and Kawasaki disease. Genital lesions may be found in herpes simplex infection, Kawasaki disease, and SJS.

Other clinical findings. Look more in associated symptoms. Lymphadenopathy may occur in rubella, infectious mononucleosis, scarlet fever, Kawasaki disease. Jaundice may be found in roseola infantum, EBV infection, Gianotti-Crosti syndrome, and leptospirosis. Hepatomegaly and/or splenomegaly may be found in EBV infection, acute HIV infection, leukaemia, juvenile chronic arthritis.

INVESTIGATIONS

Investigation of rash in childhood should initially be tailored towards possible causes and may include the following:

– culture of blood, respiratory specimens, CSF, and stool for bacteria and viruses;

– PCR: most viral exanthems can be diagnosed by PCR of blood or CSF, including the herpesviruses, measles, rubella, parvovirus B19, adenovirus, enterovirus;

– specific bacterial PCR, e.g. meningococcal or pneumococcal, or 16S PCR may be used;

– serology — IgM, paired IgG;

– antigen tests — poor sensitivity, so less frequently used, although urine pneumococcal antigen test may be useful in over 5 year olds;

– specific tests: salivary IgA or IgM for measles; immunofluorescence of vesicle fluid for varicella or herpes infections; immunofluorescence of NPAs for adenovirus.

In most studies of childhood rashes, in about half of patients no cause is identified.

Basic laboratory tests like CBC, biochemical blood test, urine test are prescribed to patients with rash and can help to specify the preliminary diagnosis. CBC test in most cases can help to determine the nature of the disease as a viral infection: influenza, measles, rubella, etc. (leukopenia, lymphocytosis, close to normal ESR), and bacterial: meningococcal, staphylococcal, streptococcal and other infections (leukocytosis, neutrophilia, increased ESR). At the same time some viral exanthems (enterovirus infection, infectious mononucleosis), especially on the first day of illness, can give leukocytosis, sometimes with neutrophilia. Atypical lymphocytes in CBC can be found in case of infectious mononucleosis; eosinophilia — with some helminthiases, allergic reactions; thrombocytosis in Kawasaki disease; thrombocytopenia in certain diseases manifested by haemorrhagic rash (e.g., thrombocytopenic purpura, meningococcemia), etc.

In many cases, pathological urine test can be found as sign of complications.

Biochemical blood tests can be useful for diagnosis of associated symptoms and complications. C-reactive protein and procalcitonin tests help to differ viral, bacterial and autoimmune aetiology.

SEMIOTICS OF SKIN LESIONS IN THE MOST COMMON INFECTIOUS AND NON-INFECTIOUS DISEASES IN CHILDREN

We highlight the importance of a proper assessment of skin lesions and correctly interpreting all clinical findings in making a diagnosis.

Maculopapular rash

A number of conditions may cause children to present with fever and maculopapular rash. These include viral and bacterial illnesses, vasculitis syndromes, and drug reactions. Many causative conditions are medical emergencies. Prompt recognition and treatment are crucial. The differential diagnosis for maculopapular rash with fever is broad. Eliciting a thorough history and physical exam is important for diagnosis. Factors to consider in any patient presenting with maculopapular rash and fever include the distribution of the patient's rash (central vs. peripheral), exposure to sick contacts, new medications and recent travel.

The following questions should be asked of all patients presenting with fever and rash as well as their caregivers:

1. Did you have any symptoms before you noticed the rash?
2. Have you noticed any associated symptoms with the rash?

3. Does anyone else around you have the same symptoms?
4. Where did the rash present? Has it changed over time?
5. Have you travelled anywhere recently?
6. Have you started any new medications recently?

The answers to these questions can help differentiate between infectious and non-infectious causes of maculopapular rash, benign conditions from emergent ones as well.

Measles (i.e., rubeola). The incubation period for measles ranges from 6 to 19 days and is followed by a prodrome of malaise, headache, and low-grade fever. This may precede or occur concurrently with cough, coryza, and conjunctivitis. During the prodrome, patients may develop Koplik spots, the typical enanthem of measles, which appear as punctate white or grey lesions on an erythematous base. Koplik spots originate on the buccal mucosa and may spread to the hard or soft palate (fig. 1).

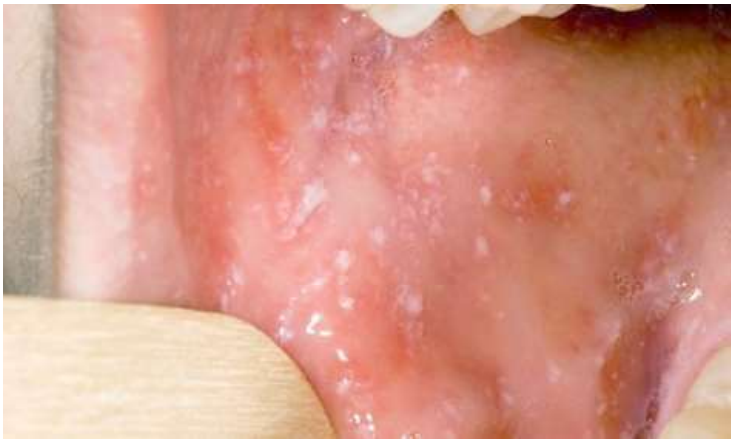

Fig. 1. Koplik spots

Approximately 4 days after the disease onset, patients will develop a high fever and an erythematous, blanching maculopapular rash (fig. 2). The typical rash originates on the patient's hairline, forehead and upper neck and spreads to the trunk and extremities over the next 3 days. The cranial to caudal progression of the rash is characteristic of measles but is not pathognomonic. After 3 to 4 days, the rash darkens to a brownish color. Coryza and conjunctivitis is typically clear with the rash, while cough may persist for next 5 days.

Immunosuppressed patients may have an atypical presentation, may not develop the characteristic rash of measles, and therefore may be challenging to recognize.

Respiratory and central nervous system complications may occur due to measles infection. 0.1 % of children develop acute encephalitis, which commonly causes permanent brain damage. 0.1–0.2 % of children expires from neurologic or respiratory complications. Seven to 10 years after primary measles infection, chil-

dren may develop subacute sclerosing panencephalitis, a rare degenerative disease of the central nervous system, which is commonly fatal. This may present with seizures and behavioral changes in a child who was previously infected with measles.

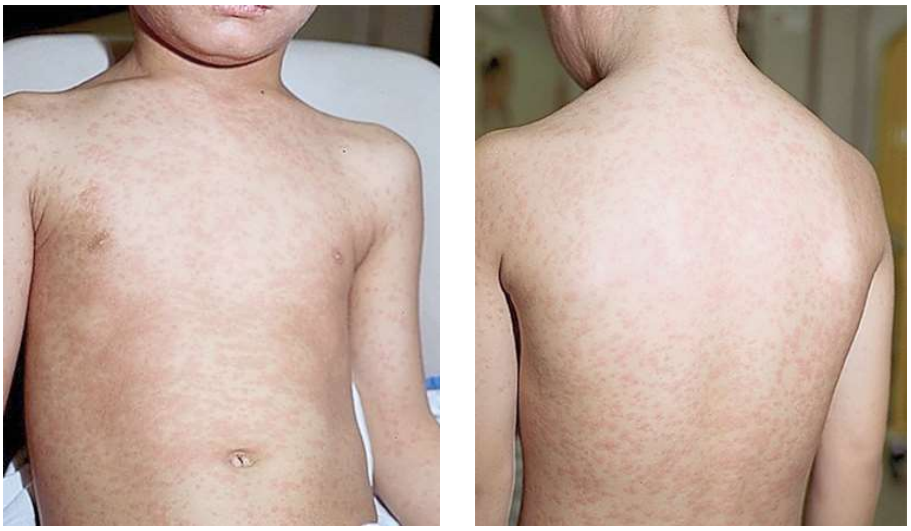

Fig. 2. Maculopapular rash in measles

Rubella (i.e., German measles) is typically mild in infants and children. Up to 50 % of infections in this age group may be asymptomatic. The prodrome for rubella presents with malaise and adenopathy in the posterior auricular, posterior cervical and sub-occipital lymph nodes (fig. 3).

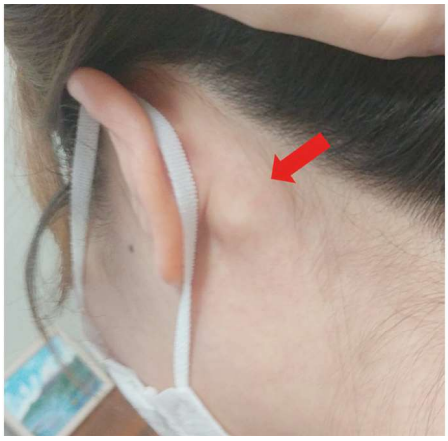

Fig. 3. Posterior auricular lymphadenopathy in rubella

Forchheimer spots, the enanthem for rubella, occurs in 20 % of patients and consists of petechiae on the soft palate (fig. 4). It may occur during the prodrome or with the onset of the rash. These spots are not specific to rubella and can be seen in cases of measles, scarlet fever, and other systemic infections. However, in combination with clinical information, the presence of Forchheimer spots supports a diagnosis of rubella and indicates diagnostic testing and infection prevention efforts.

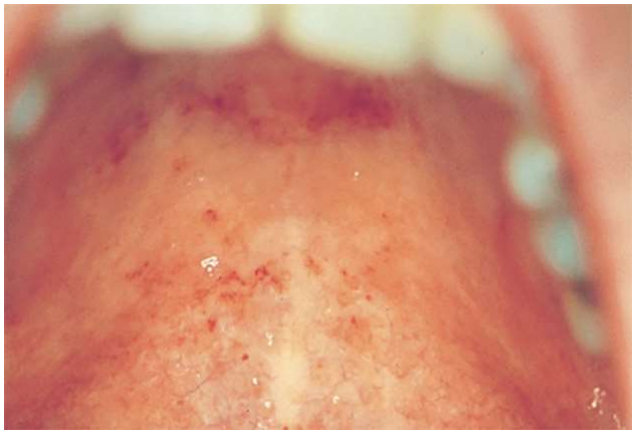

Fig. 4. Forchheimer spots

In children, a prodrome may not be present. The rash may be the first manifestation. The exanthem for rubella consists of pink macules and papules 1 to 4 mm in diameter (fig. 5) and originates on the face, neck, and scalp with subsequent extension to the trunk and extremities, and becomes generalized within 24 hours. It may occur with fever, myalgias, and arthralgias. The rash is usually evident for about three days but may last anywhere from one to eight days. Mild non-exudative conjunctivitis also may be observed.

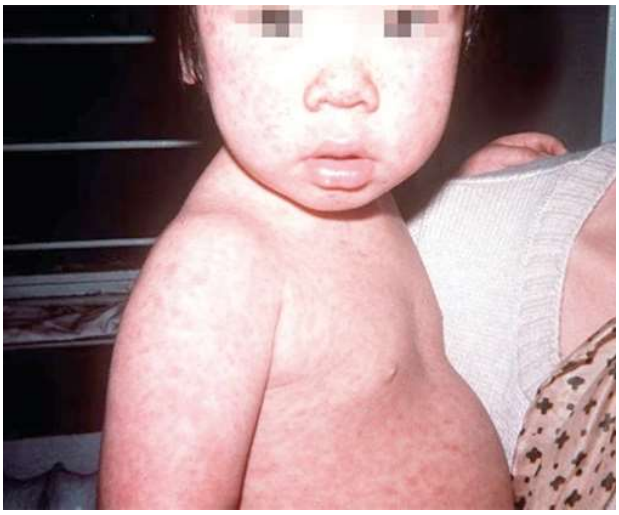

Fig. 5. Rubella rash

Complications of rubella are not common. They include arthritis, which occurs primarily in women and increases in incidence with age, and rarely thrombocytopenia and encephalitis.

An infected pregnant woman may infect the fetus that can develop Congenital Rubella syndrome. Although CRS is classically characterized by a fetal triad of congenital cataracts, deafness, and patent ductus arteriosus, multiple fetal organs may be involved. In babies who contracted rubella in the womb a distinctive rash

can occur. It presents as blue, purple, or dark spots on the face and body. The rash resembles the appearance of a blueberry muffin. These lesions indicate cutaneous haematopoiesis and may occur in other intrauterine infections and haematologic disorders (fig. 6). The incidence of CRS depends upon the time when the mother contracts rubella. CRS impacts 50 % of women infected in the first 12 weeks of pregnancy. This falls to 25 % for women infected between weeks 13 and 24 of pregnancy. Infection after 24 weeks of pregnancy rarely causes CRS.

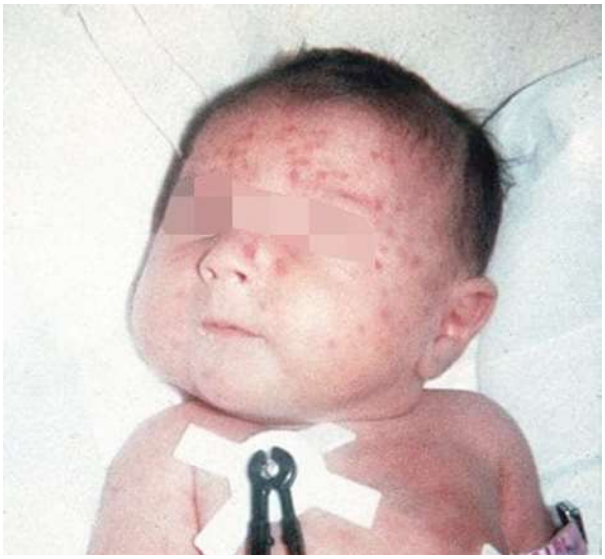

Fig. 6. Blueberry muffin newborn with lesions on the forehead

Erythema infectiosum (i.e., fifth disease). Infection with parvovirus (i.e., erythrovirus) B19 in immunocompetent children is typically mild. Patients may develop a low-grade fever. One to 4 days after the onset of fever, the characteristic exanthem induced by parvovirus B19 may appear. At this time, children are typically afebrile. The exanthem starts as an erythematous facial rash (fig. 7), also known as a «slapped cheek» rash. After 1 to 4 days, the rash becomes maculopapular and spreads to the trunk and extremities (fig. 8). Central clearing of the rash may give it a reticular, lace-like appearance. The rash on the trunk and extremities persists for 1 to 6 weeks. During this time, the intensity of the rash may vary with exposure to sunlight or heat.

Arthralgias following infection with parvovirus B19 occur in 8 % of children but are more common in adolescents and adults. In children, arthralgias characteristically involve the knees and ankles. Parvovirus B19 can precipitate aplastic crises in patients with chronic hemolytic anemias, such as those due to sickle cell disease or hereditary spherocytosis. These patients less commonly develop a rash but may present with such clinical findings as anemia, pallor, or malaise, following a mild febrile illness.

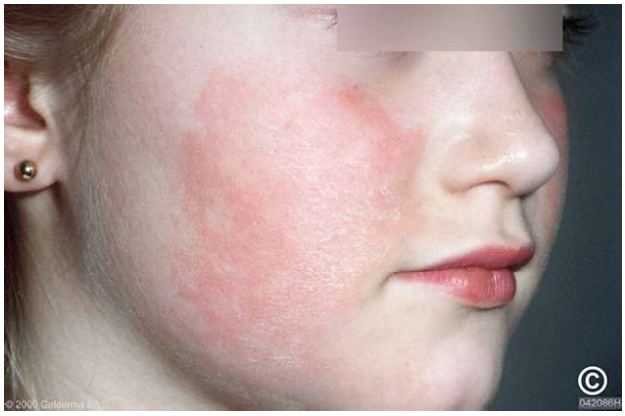

Fig. 7. «Slapped cheek»

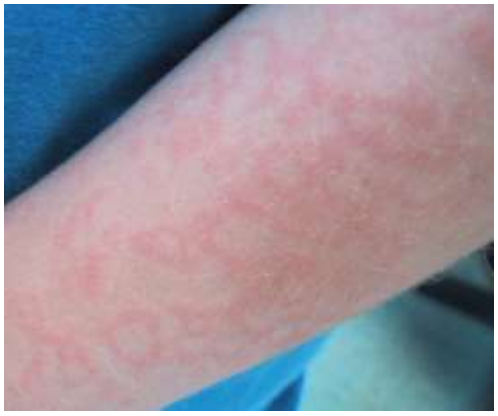

Fig. 8. Pathognomonic reticulated, lacy-appearing eruption of fifth disease

The most severe complication of parvovirus B19 infection is fetal loss that can occur in 5–10 % of infected pregnant women. Fetuses may develop hydrops fetalis as a result of maternal infection.

The majority of primary infections with HHV-6 are asymptomatic or subclinical, presenting with a non-specific low-grade fever. The classic presentation of **roseola infantum (i.e., exanthem subitum)** occurs in 20 % of children infected with HHV-6. Roseola has an incubation period of 9 to 10 days. The disease first presents with a high fever (38.9 °C to 40.5 °C) that lasts for three days. Roseola induced febrile seizures are common in patients and are reported to be the aetiology of 33 % of febrile seizures and recurrent febrile seizures seen in emergency rooms. The exanthem of roseola may occur concurrently with the fever or after the fever subsides. The rash consists of discrete pale, pink macules 1 to 5 mm in diameter, which commonly originates on the trunk, neck and behind the ears and spread to the proximal extremities (fig. 9).

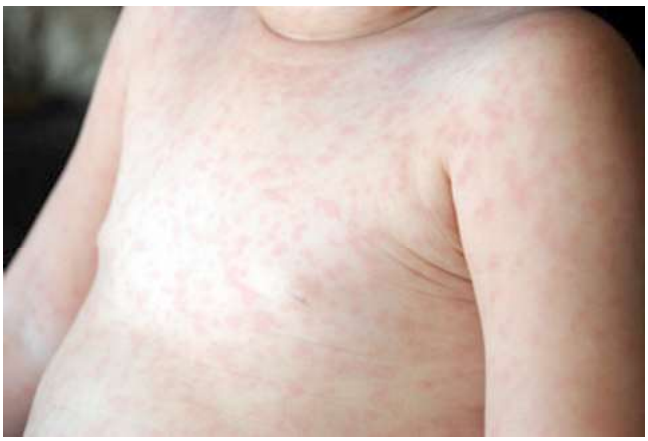

Fig. 9. Roseola rash

It commonly spares the face and distal extremities. The rash lasts between 2 to 48 hours, may become confluent and may be preceded by an enanthem of erythematous papules on the soft palate and uvula (Nagayama spots) in two-thirds of patients (fig. 10).

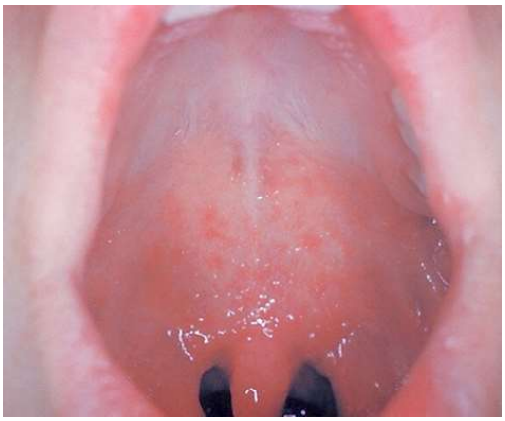

Fig. 10. Nagayama spots

In immunocompromised patients, HHV-6 may reactivate, causing a number of manifestations including rash, hepatitis, pneumonia, and encephalitis.

Symptoms of **Epstein-Barr virus infectious mononucleosis** typically present 4 to 6 weeks after infection with EBV. The prodrome consists of usually severe persistent fatigue and myalgias and typically lasts one to two weeks. Following the prodrome, patients present with cervical lymphadenopathy, fever, severe sore throat due to pharyngeal inflammation, hepatomegaly, and splenomegaly. A generalized maculopapular, urticarial, or petechial rash may also be seen in some patients. The characteristic exanthem is a maculopapular rash, which involves the trunk and arms. It appears shortly after the onset of symptoms, lasts for 1 to 6 days, and is identified in 3 to 15 % of patients, especially after the administration of ampicillin or amoxicillin (fig. 11).

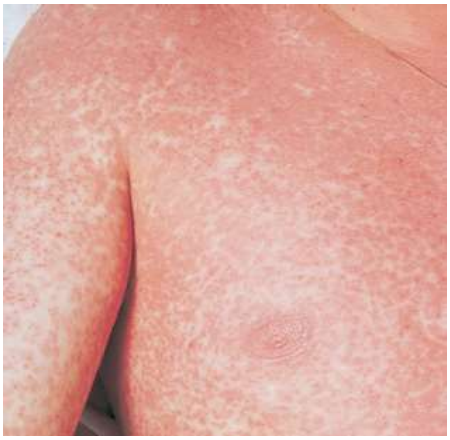

Fig. 11. Characteristic rash of EBV Infectious mononucleosis

Complications from infectious mononucleosis are rare but may include splenic rupture, hepatitis, myocarditis, and central nervous system dysfunction secondary to meningitis or encephalitis. Ten per cent of patients will develop persistent fatigue that lasts for more than 6 months.

Enterovirus infections. More than 90 % of infections caused by the non-polio enteroviruses are asymptomatic or result only in an undifferentiated febrile illness. When a more serious disease occurs, the clinical spectrum and disease severity vary with the age, sex, and immune status of the host. Some clinical syndromes (e.g., viral meningitis and some exanthems) are caused by numerous enterovirus serotypes, while others appear limited to specific enterovirus subgroups (e.g., HFMD with enterovirus A71, some group A coxsackieviruses, and pleurodynia and myocarditis with the group B coxsackieviruses). HFMD is discussed in detail separately (see “Vesicular-bullous rash” below).

Coxsackieviruses and echoviruses cause a variety of exanthems, which are sometimes associated with enanthems. Except for HFMD, these eruptions may mimic other known causes of rash illness and are not sufficiently distinctive in appearance to permit reliable aetiologic diagnosis on clinical grounds alone (fig. 12).

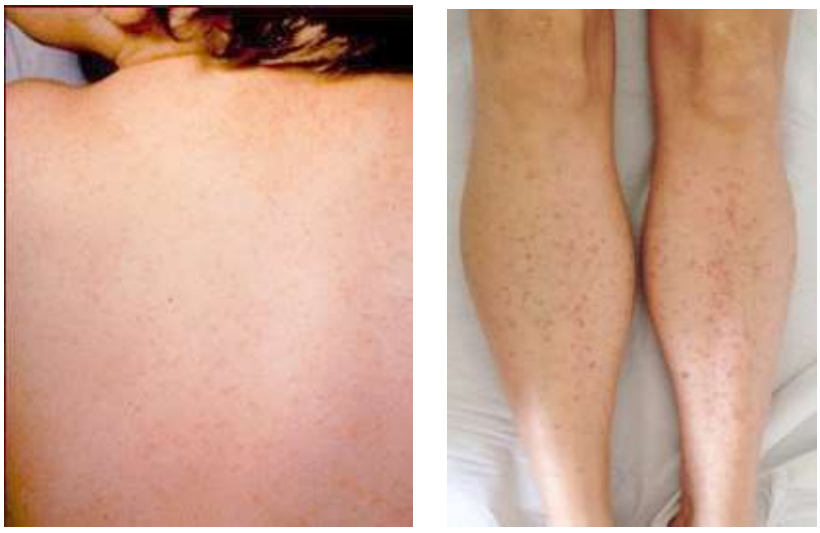

Fig. 12. Maculopapular exanthem in Echovirus infection

Generalized maculopapular eruptions commonly occur with enterovirus infections, particularly those due to echoviruses. Most cases are non-specific and cause the patient little or no distress. The prototypic «Boston exanthem» is characteristic of these rash illnesses, in which multiple cases of mild illness occur sequentially in households with young children. Fever lasts 24 to 36 hours and then declines simultaneously with the appearance of discrete, non-pruritic, salmon-pink macules and papules of approximately 1 cm diameter usually on the face and upper chest.

Acute HIV (i.e., acute retroviral syndrome). HIV infection may present as a mononucleosis type of syndrome with a constellation of non-specific symptoms. Without a high degree of suspicion, the diagnosis can be missed frequently by clinicians. In some cases, early HIV infection may be asymptomatic. A generalized rash is also a common finding in symptomatic acute HIV infection. The eruption typically occurs 48 to 72 hours after the onset of fever and persists for five to eight days. The upper thorax, collar region, and face are most often involved, although the scalp and extremities, including the palms and soles, may be affected. The lesions are characteristically small (5 to 10 mm), well-circumscribed, oval or round, pink to deeply red colored macules or maculopapules. Vesicular, pustular, and urticarial eruptions have also been reported but are not nearly as common as a maculopapular rash. Pruritus is unusual and only mild when present. Oral ulcerations may be present.

Scarlet fever presents with sudden onset of fever and malaise 2 to 3 days after infection. Patients may have pharyngitis or tonsillitis. The tongue develops enlarged papillae, which initially appear furry and then become erythematous, resulting in a strawberry tongue appearance. The characteristic rash of scarlet fever is typically seen 2 days after the onset of infection. The scarlet fever rash first appears as tiny red bumps on the chest and abdomen that may spread all over the body, resulting in a diffuse erythema that blanches with pressure, with numerous small (1 to 2 mm) papular elevations, giving a «sandpaper» quality to the skin (fig. 13). The rash is slight pruritic, most marked in the skin folds of the inguinal, axillary, antecubital, and abdominal areas and about pressure points. It often exhibits a linear petechial character in the antecubital fossae and axillary folds, known as Pastia's lines. Rash lasts about two to five days and results in desquamation.

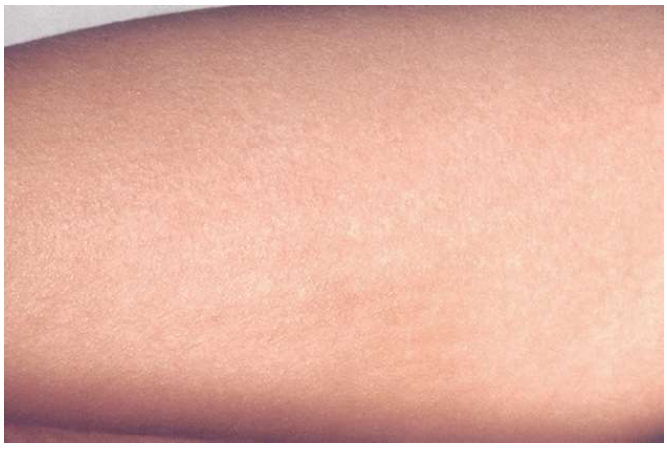

Fig. 13. Scarlet fever rash on the volar surface of the forearm

Complications from scarlet fever include suppurative such as peritonsillar and retropharyngeal abscesses, cervical lymphadenitis and non-suppurative — acute rheumatic fever, post-streptococcal glomerulonephritis, and paediatric au-

toimmune neuropsychiatric disorders. Prompt antibiotic treatment may decrease the risk of developing any complications, and shorten the duration of symptoms by approximately 16 hours.

Major manifestations of **Yersinia pseudotuberculosis infection** include fever, scarlatiniform rash, acute gastroenteritis, and abdominal symptoms. Acute pseudoappendiceal abdominal pain is common, resulting from ileocecal mesenteric adenitis or terminal ileitis. Other uncommon findings are intestinal intussusception, EN, septicemia mainly in individuals with underlying conditions, acute renal failure with nephritis, and sterile pleural and joint effusions. Clinical features can mimic those of Kawasaki disease.

Cutaneous manifestations at the disease onset include erythema of the face, neck, toes, and hands; these signs have become known as “hood,” “gloves,” and “socks”, conjunctival hyperemia, pale nasolabial triangle, strawberry tongue, scarlet fever-like rash. The rash has variable presentations being punctuate (rubella or measles-like) or confluent (erythematous-like) (fig. 14). EN can occur with relapse; desquamation on earlobes, hands, palms, feet, and trunk appears during the recovery period. Skin lesions can also be associated with Yersinia enterocolitica infection.

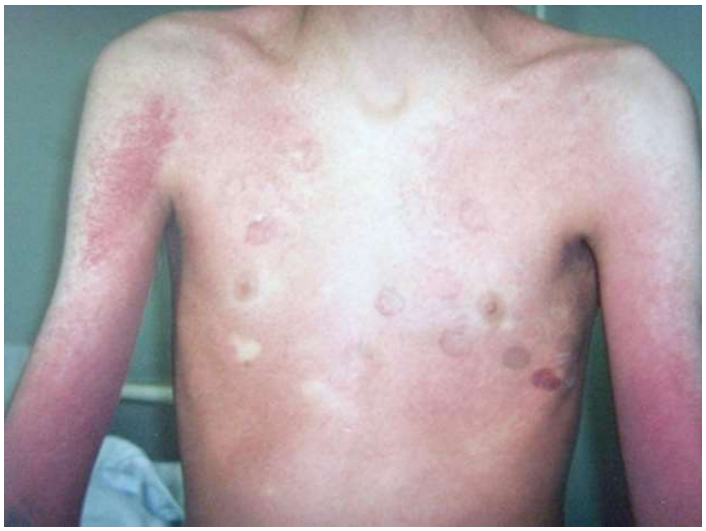

Fig. 14. Scarlet fever-like rash in yersiniosis

A maculopapular eruption resembling a wide variety of viral exanthems, particularly rubella, can be an early finding in **meningococcemia**. This transient rash generally does not persist for more than two days and has frequently disappeared hours after its first observation; it is neither purpuric nor pruritic. Meningococcemia is discussed in detail separately (see “Haemorrhagic rash” below).

Mycoplasma pneumoniae is a frequent cause of upper and lower respiratory tract infections in children, including pharyngitis, acute bronchitis, and pneumonia.

Mucocutaneous and cutaneous manifestations of M. pneumoniae infection include erythematous maculopapular or vesicular rashes, urticaria, erythema multiforme, SJS, and mucositis. Concurrent or antecedent respiratory symptoms are often present but not always prominent. Rashes are often mild and self-limiting. They are reported to accompany approximately 17 % of respiratory tract infections and can be confused with hypersensitivity reactions to antibiotics.

Erythema multiforme caused by M. pneumoniae is similar to other forms of this syndrome but more frequently occurs with mucosal and respiratory tract involvement (fig. 15). While SJS is an uncommon manifestation of M. pneumoniae infection, M. pneumoniae appears to be among the most common infectious causes of SJS (fig. 16). Among patients with SJS due to M. pneumoniae, concurrent pneumonia is more common than mild upper respiratory tract infection. M. pneumoniae-associated mucositis is a syndrome characterized by erosive oral, ocular, and genital lesions that occurs most often in children (fig. 17).

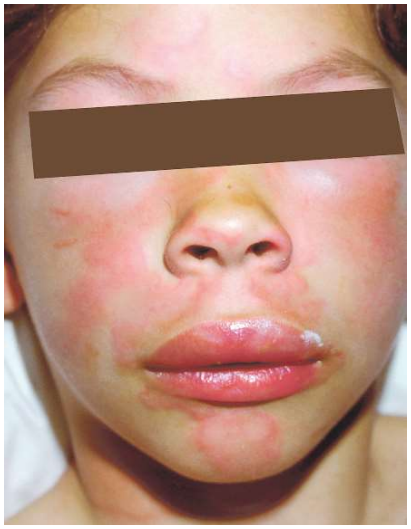

Fig. 15. Erythema multiforme associated with M. pneumoniae

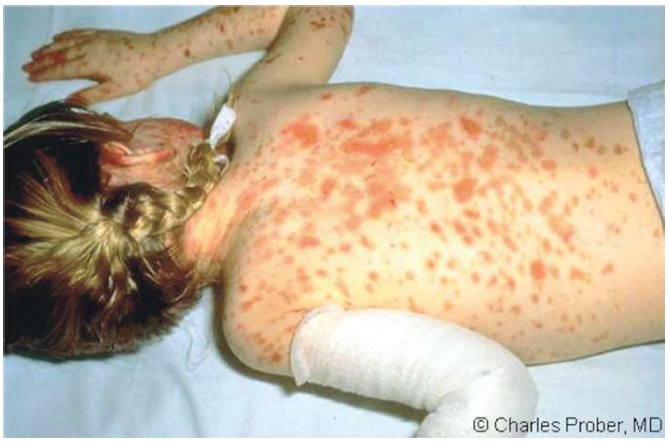

Fig. 16. Erythema multiforme rash (Stevens-Johnson syndrome) associated with M. pneumoniae

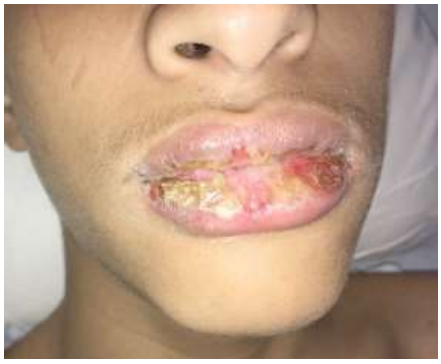

Fig. 17. Typical oral oedema, ill-defined erosions, and crusting in a patient with MIRM

Exanthematous Drug Reactions

Exanthematous drug eruptions typically present 4 to 21 days after the initiation of a new medication and evolve rapidly. They consist of symmetric erythematous macules and papules, which start on the trunk and intertriginous areas. The lesions may be pruritic and are commonly associated with a low-grade fever (< 38.5°C). Mucous membranes are not characteristically involved. Most drug eruptions fade within a week of discontinuation of the offending drug. A high-grade fever (> 38.5 °C), mucous membrane involvement or lymphadenopathy may be indicative of a more serious evolving reaction including SJS, toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms.

HHV-6/7 reactivation has been reported in drug reaction with eosinophilia and systemic symptoms (fig. 18). DRESS is a life-threatening multi-organ adverse drug reactions characterized by maculopapular rashes developing > 3 weeks after starting with a limited number of drugs, prolonged clinical symptoms after discontinuation of the causative drug, fever (> 38 °C), liver abnormalities, leukocyte abnormalities (at least one between leukocytosis [> 11 × 10^9/L], atypical lymphocytosis [> 5 %], eosinophilia [> 1.5 × 10^9/L]), lymphadenopathy.

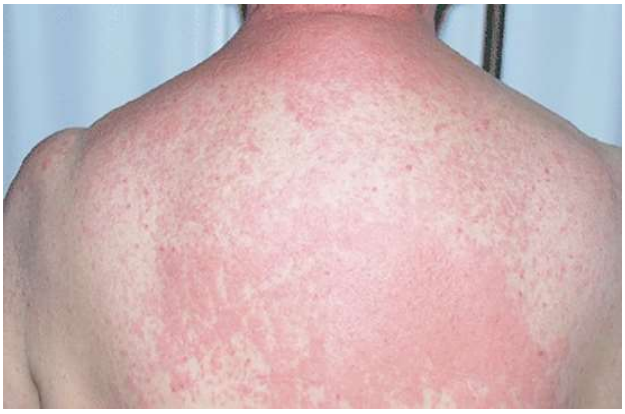

Fig. 18. Maculopapular eruption of the trunk in DRESS associated with HHV-6 reactivation

Maculopapular drug reactions can mimic viral exanthems, such as measles, rubella, parvovirus B19, chikungunya, zika, and even varicella (when vaccinated persons exhibit symptoms), so it is critical for clinicians to take a thorough history and identify any new drugs that the patient may be taking. Resolution of the rash after cessation of the suspected drug may also help identify the causative medication. The reaction will typically resolve within two weeks of withdrawal of the causative drug, but it has been reported to resolve slower over the course of many weeks.

Erythema nodosum

Erythema nodosum is the most common form of septal panniculitis (inflammation of the subcutaneous fat) resulting from a hypersensitivity reaction in response to numerous antigens or triggers. Infection is the most commonly identified aetiology, with Group A β-hemolytic streptococcal infection the most common cause. Other bacterial causes include Yersinia enterocolitica, Yersinia pseudotuberculosis, Salmonella, Campylobacter jejuni, Mycoplasma pneumoniae, and Chlamydia species, among protozoal causes — Giardia lamblia, Entamoeba histolytica, and Toxoplasma gondii. Viral causes include EBV, cytomegalovirus, hepatitis B virus, hepatitis C virus, parvovirus B 19, and HIV. EN may also occur secondary to drugs (e.g., oral contraceptives, sulfonamides, aspirin, and penicillin), inflammatory bowel disease, malignancy, sarcoidosis, pregnancy, and other conditions. In approximately 50 % of cases, no cause can be found and the condition is deemed idiopathic.

EN occurs in all ages with highest rate between 18 and 34 years of age, predominantly in women (the female to male ratio is 3–5:1). In the paediatric age group, both sexes are equally affected.

Classic EN presents with a sudden onset of tender, erythematous/violaceous, warm, round or oval, subcutaneous nodules occurring primarily on the pretibial area, and less commonly, on the knees and ankles. Rarely, other areas of the body such as arms, forearms, thighs, calves, buttocks, trunk, and face may be affected (fig. 19). Lesions are usually bilateral and symmetrical, ranging from 0.5 to 6 cm in diameter. Nodes on palpation are painful, deeply located, and sometimes merge with each other. EN is often preceded or accompanied by a low-grade fever, malaise, fatigue, and arthralgias. Over time, the lesions tend to become bruise-like with a greenish or yellow discoloration and resolve without atrophy, ulceration, necrosis or scarring in 2–8 weeks. New nodules can continue to arise for as long as 6 weeks.

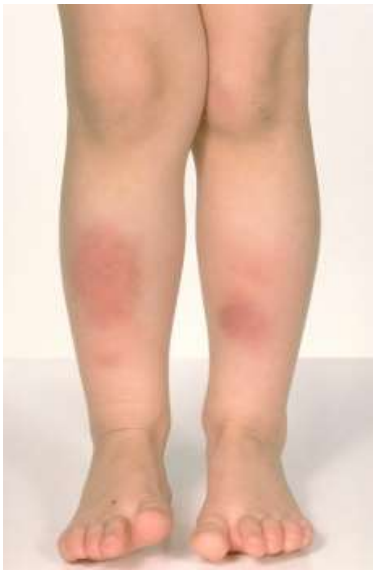

Fig. 19. Erythematous, oval, subcutaneous nodules on bilateral shins in erythema nodosum

Papular-purpuric gloves and socks syndrome

Papular-purpuric gloves and socks syndrome is a syndrome observed in exanthematous diseases, which, despite the various causative agents, has a similar clinical presentation. PPGSS manifests as redness and oedema of the hands and feet followed by the appearance of petechial and/or purpuric lesions on the palms and soles (fig. 20, 21). It is estimated that PPGSS is most often associated with parvovirus B19, but is also reported with hepatitis B virus, CMV, EBV, VZV, HHV-6, Mycoplasma pneumoniae, Yersinia, measles, rubella, coxsackie virus B, or drug reactions (e.g., co-trimoxazole).

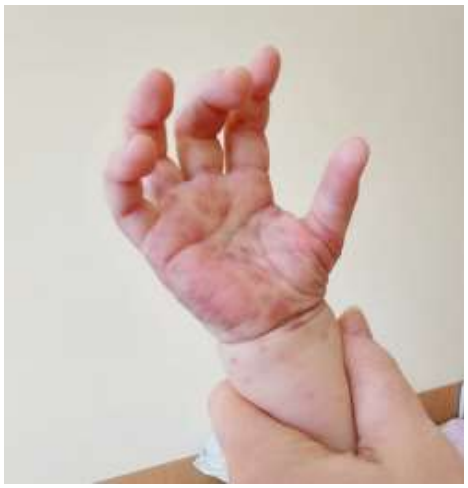

Fig. 20. Papular-purpuric rash on the hand of a child with EBV infection

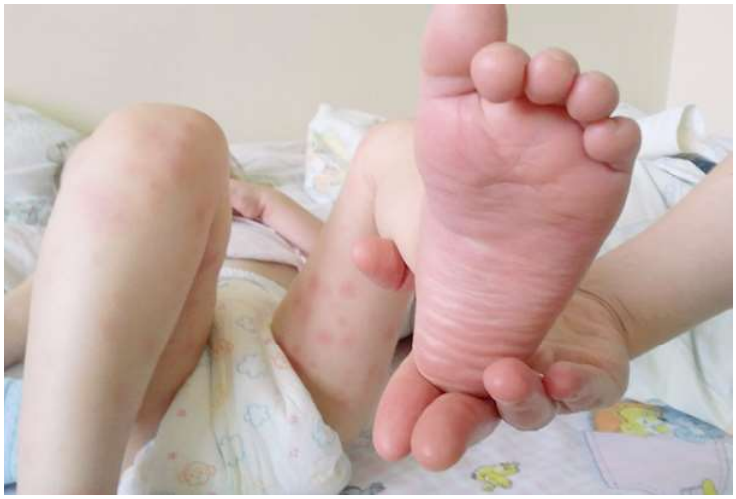

Fig. 21. Papular-purpuric gloves and socks syndrome in a child with enterovirus infection

Initially there is a symmetrical, painful erythema and oedema of the hands and feet, with rapid progression to petechiae and/or purpura on the palms and soles. Vesiculae and bullae may develop, with subsequent skin sloughing. There is often a sharp cut-off at the wrists or ankles, but other areas, including the cheeks, elbows, knees, inner thighs, buttocks, and vulva, may also be affected. Spontaneous resolution occurs without long-term sequelae in several weeks.

Haemorrhagic rash

Haemorrhagic rashes include a very wide range of heterogeneous conditions resulting from infectious, non-infectious, reactive, or autoimmune processes. Owing to extravasated erythrocytes, haemorrhagic rash (petechiae, purpura, or ecchymosis) do not blanch when pressure is applied.

"Glass test" can be used to assist with assessing whether a rash is blanching — a drinking glass can be applied firmly against a rash — if the rash does not disappear, it is non-blanching.

Haemorrhagic rash is accompanied by bacterial (meningococcemia, as well as sepsis, caused by Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae, Listeria monocytogenes, Neisseria gonorrhoeae), viral (influenza, enterovirus, EBV infection, CMV infection, atypical measles, haemorrhagic fevers), parasitic (malaria) infections, and rickettsioses (Rocky Mountain spotted fever, epidemic typhus). The majority of children with petechiae do not have a serious bacterial infection or meningococcal disease, and often will not have a specific cause identified. For instance, mechanical causes, such as coughing, vomiting, crying, or local physical pressure (tight tourniquet, being held tightly for procedures, stroller straps, car seats, etc.) can be quite common.

Influenza is not a common cause of rash, and a rare cause of petechial exanthem. Typically, rash appears on the 1–2 day of the disease onset, it involves mainly the trunk and face, scattering in the extremities, and resolves within 2–5 days. Influenza can also be accompanied by petechial enanthem on the soft palate, which is not specific for influenza and can be seen in cases of rubella, measles, scarlet fever, EBV infection. Other haemorrhagic manifestations are possible: epistaxis, subconjunctival haemorrhages, blood in the sputum, etc.

When making a differential diagnosis, attention should be paid to the presence of the characteristic clinical manifestations of influenza: fever, chills, headache, sore throat, myalgia, and dry cough.

The main life-threatening infectious causes of haemorrhagic exanthem in young children are **meningococcemia**, less often pneumococcemia, and Haemophilus influenzae type b bacteremia.

Within the first 4–6 h of the onset of meningococcal disease, children have non-specific features such as fever, poor feeding or decreased appetite, nausea, vomiting, and irritability. The first classic symptom of MD is rash, which sometimes evolves from non-specific (e.g., macular or maculopapular) to petechial and purpuric over several hours. Petechial rash appears on the 1–2 day of the disease onset, sometimes within 2–12 h, as discrete lesions 1 to 2 mm in diameter, most frequently on the trunk and lower portions of the body. Petechiae can coalesce into larger purpuric and ecchymotic lesions (fig. 22). Haemorrhagic rash correlates with the degree of thrombocytopenia and clinically are important as an indicator of the potential for bleeding complications secondary to disseminated intravascular coagulopathy. Extensive skin lesions can lead to subsequent full thickness skin loss and deep muscle damage (fig. 23). The majority of children with meningococcemia have one of the three signs of sepsis — leg pain, abnormal skin color (e.g., pallor or mottling), cold hands and feet at a median time of 8 hours after the onset of illness.

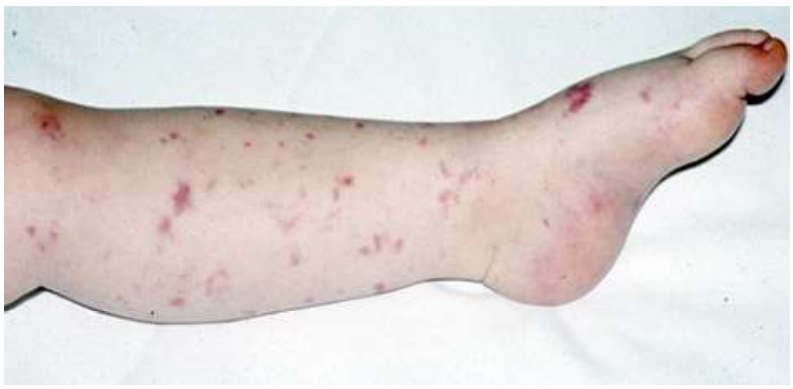

Fig. 22. Petechial and purpuric rash in meningococcemia

Fig. 23. Fingertip necrosis in meningococcemia

Early diagnosis is a very important condition for the effective treatment and mortality reductions in MD. Therefore, in doubtful cases, preventive admission to hospital or repeated clinical examination within 4–6 h should be done.

Rocky Mountain spotted fever is transmitted via tick bite from April to September and begins with malaise, headache, myalgia, arthralgia, high-grade fever, and chills. The clinical spectrum of human infection ranges from mild to fulminant disease. The incubation period is 3–12 days. The onset of symptoms may be gradual or abrupt. Typically, a rash appears on the 3–5 day of illness as a blanching erythematous rash with macules (1 to 4 mm in size) that become petechial over time (fig. 24, 25). The lesions start on the wrists, ankles, palms, soles, and forearms and rapidly extend to the neck, face, axillae, buttocks, and trunk. Characteristic features are swelling of the eyelids and limb oedema (fig. 24). Urticaria and pruritus are not characteristic of RMSF, and their presence makes the diagnosis unlikely. Some patients with RMSF never develop a rash. Neurologic symptoms include severe headache, restlessness, insomnia, delirium, and coma due to encephalitis. The cerebrospinal fluid analysis often shows a white blood count of < 300 cells per microL with lymphocytic predominance, a normal glucose level and moderately elevated protein level. As a rule, there is moderate thrombocytopenia and neutrophilic leukocytosis. The presence of hyponatremia may be a diagnostic clue to the possibility of rickettsial disease. Hyponatremia is a particularly common finding in patients with central nervous system involvement.

Major complications of RMSF include encephalitis, non-cardiogenic pulmonary oedema, acute kidney failure, adult respiratory distress syndrome, cardiac arrhythmias, coagulopathy, gastrointestinal bleeding, and skin necrosis.

Ehrlichiosis is also transmitted through the bites of infected ticks. The clinical manifestations are non-specific and associated with flulike symptoms — fever, headaches, myalgias and arthralgias. A skin eruption occurs in two-thirds of children and can be maculopapular, petechial, or characterized by diffuse erythro-

derma, typically spares the face, palms, and soles. Nausea, vomiting, abdominal pain, and cough are variably present. Patients can develop neurologic disorders, such as aseptic meningitis or meningoencephalitis. Pancytopenia is a hallmark laboratory feature of ehrlichiosis early in the course of the illness with largest decline in lymphocyte population. Ehrlichial disease is often accompanied by thrombocytopenia.

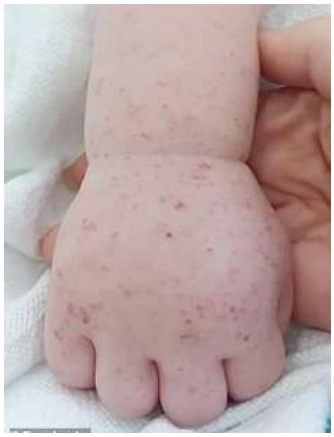

Fig. 24. Petechial rash and hand oedema in a 2-year old child

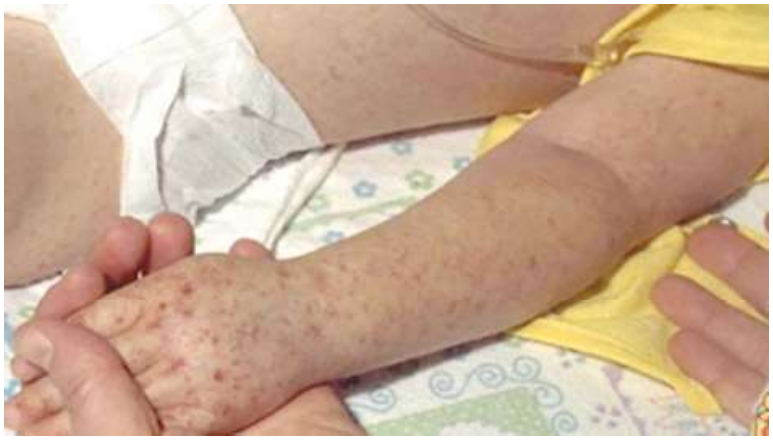

Fig. 25. Haemorrhagic rash in a child with RMSF

Rarely does it present as a multi-system disease resembling toxic or septic shock syndrome with multi-organ failure rarely. Other life-threatening manifestations include cardiovascular failure, haemorrhages, hepatic insufficiency or failure, interstitial pneumonia, and adult respiratory distress syndrome.

The cause of haemorrhagic rash can be **viral haemorrhagic fevers** — a group of highly virulent illnesses, caused by four families of RNA viruses: Arenaviridae, Filoviridae, Bunyaviridae, and Flaviviridae. VHFs are distributed worldwide and are often associated with high morbidity and mortality (up to 90 %). Many of them are transmitted via mosquito bites (Brazilian, yellow, dengue fever, etc.), and some via contact with rodents (e.g., Lassa fever, haemorrhagic fever with renal syndrome) and fruit bats (Marburg and possibly Ebola disease). When a person encounter an infected animal or insect, the virus can spread through spillover into the human population, and subsequently is transmitted from person-to-person through contact with blood or other body fluids.

VHFs have a similar clinical course. The onset of illness is typically abrupt with high-grade fever, chills and non-specific symptoms, which include anorexia, weakness, headache and myalgia. Gastrointestinal symptoms, namely nausea, vomiting, diarrhoea and abdominal pain, are often present in the prehaemorrhagic stage, which lasts for approximately three to seven days. VHFs may also mimic intraabdominal surgical emergencies. Haemorrhagic manifestations, the hallmark of

Ebola and Marburg haemorrhagic fevers and full-blown Crimean-Congo haemorrhagic fever, occur in less than 20 % of cases of Lassa fever. Haemorrhages usually concern multiple sites, including ecchymoses, bleeding at injection site, gingival haemorrhage, haematemesis and melena. Death almost always occurs in the context of shock and multi-organ failure six to eight days after the onset of symptoms in cases of Ebola haemorrhagic fever, six to 10 days in cases of Crimeane-Congo haemorrhagic fever, and within the second week in cases of Lassa fever and Marburg haemorrhagic fever.

The first reported outbreak of ***Ebola virus disease*** (i.e., Ebola haemorrhagic fever) took place in 1976 in the Democratic Republic of the Congo and Sudan. Since then, outbreaks have been observed in Gabon, the Republic of Guinea, Liberia, Mali, Nigeria, Sierra Leone, Sudan, and Uganda. Cases of ***Marburg virus disease*** (i.e., Marburg haemorrhagic fever) were reported in the following countries: Angola, the Democratic Republic of the Congo, Germany, ex-Yugoslavia, South Africa, Kenya and Uganda. The incubation period of the illnesses ranges from 2 to 21 days. Younger children appear to have shorter mean incubation periods than adults. Younger children also have a more rapid disease course including shorter time from symptom onset to hospitalization as well as from onset of symptoms to death. The mortality rate is especially high for children younger than 5 years of age. During early infection (days 1–3 following disease onset), patients present with a non-specific febrile illness (symptoms may include anorexia, arthralgia, headache, malaise, myalgia) that progresses in the first week to severe gastrointestinal symptoms and signs (nausea, vomiting and high-volume diarrhea in Ebola virus disease). Around the fifth day after the onset of symptoms, morbilliform, maculopapular, petechial, and ecchymotic rashes, most prominent on the trunk (chest, back, stomach), can occur. As the viral load increases, typically the severity of clinical manifestations increases as well. During the terminal phase (days 7–12 following disease onset), tissue hypoperfusion and vascular leakage, often in conjunction with dysregulated inflammation, lead to multiple organ dysfunction syndrome and/or damage, including acute kidney injury.

The non-specific signs and symptoms especially early in the course of VHFs render it difficult to differentiate them from other infectious diseases on clinical grounds alone. Thus, a high index of suspicion and a detailed epidemiological history, taking into account travel destinations, exposures and incubation periods, are imperative.

Thrombocytopenia due to HIV infection, acquired rubella and CMV infection, infectious erythema) or other infectious agents may present with petechiae or purpura (infectious mononucleosis, adenovirus infection). A newborn with congenital infection (rubella, syphilis, toxoplasmosis, CMV or parvovirus B19 infection) may have haemorrhagic exanthem. Thrombocytopenia is often noted during bacterial septicemia as a part of disseminated intravascular coag-

ulation. This syndrome can also be caused by a severe viral, fungal, or parasitic infection.

Petechiae can also be the result of **thrombocytopenia in some non-infectious diseases** (immune thrombocytopenic purpura, haemolytic uremic syndrome, thrombotic thrombocytopenic purpura), as well as platelet dysfunction due to drug therapy. Some non-communicable diseases may characterized by a normal platelet count but present with a haemorrhagic rash. For instance, ***Schonlein-Henoch purpura (i.e., IgA vasculitis).*** The skin manifestation of IgA vasculitis is palpable purpura symmetrically distributed in the lower extremities and sometimes the upper limbs and trunk. The absence of thrombocytopenia is important for making diagnosis. ***The syndrome of acquired platelet dysfunction with eosinophilia*** (i.e., non-thrombocytopenic purpura with eosinophilia) occurs in children and young people from South-East Asia and manifests with widespread spontaneous bruising on the extremities, body and face, and are characterized by prolonged clotting time, normal platelet count, and eosinophilia.

Vesicular-bullous rash

Vesicular-bullous rash is observed in infectious diseases caused by HSV, VZV, enteroviruses. In addition, these morphological elements of rash are typical for staphylococcal scalded skin syndrome, congenital syphilis. Moreover, non-infectious causes may present with a vesicular-bullous rash — epidermolysis bullosa, miliaria, nutritional deficiencies, and some types of eczema.

Neonatal Herpes simplex virus infection is rare. It primarily results from intrapartum exposure to maternal cervical or vaginal lesions or by an ascending infection, sometimes through apparently intact membranes. Postnatal inoculation may also occur but is less common.

The risk of HSV transmission to a neonate born to a mother who acquires primary genital infection near the time of delivery is estimated to be 25 % to 60 %. In contrast, the risk to a neonate born to a mother shedding HSV because of reactivation of infection acquired during the first half of pregnancy or earlier is less than 2 %. History of maternal genital HSV infection is not helpful in diagnosing neonatal HSV disease because primary and recurrent genital infections may be asymptomatic or associated with non-specific findings (e.g., vaginal discharge, genital pain or shallow ulcers).

Clinical presentation of HSV infection in newborns usually develops in one of three patterns:

– localized to the skin, eyes, and mouth (fig. 26);

– central nervous system disease;

– disseminated disease involving multiple organs (most often liver, lungs and central nervous system).

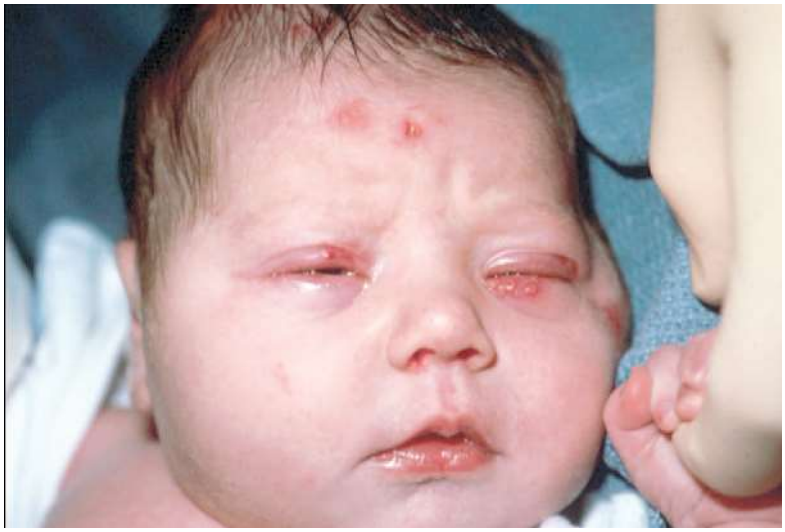

Fig. 26. Skin, eyes and/or mouth disease

Initial signs of HSV infection can occur anytime between birth and approximately 6 weeks of age, although almost all infected infants develop clinical disease within the first month of life. Infants with disseminated disease and skin, eyes and/or mouth disease (SEM) have an earlier age of onset, typically presenting between the first and second weeks of life. Infants with CNS disease usually present with illness between the second and third weeks of life.

Skin lesions occur in the majority of patients and may be present in all three infection patterns. The skin lesions typically consist of clusters of 1 to 3 mm vesicles and erythematous papules that may develop into pustules, crusts, and erosions. They usually occur on the scalp or face. Lesions also may occur on the trunk or buttocks (especially with a breech presentation).

Primary **herpetic gingivostomatitis** typically occurs in children between six months and five years of age, but it can occur in older children and adolescents. Acute gingivostomatitis is the most common manifestation of primary HSV infection. It occurs in 13 to 30 percent of affected children. Primary herpetic gingivostomatitis is characterized by ulcerative lesions of the gingiva and mucous membranes of the mouth, often with perioral vesicular lesions. Herpetic gingivostomatitis occurs approximately one week after contact with an infected child or adult (the contact case often is asymptomatic). It generally begins with a prodrome that lasts approximately four days and may include fever (> 38 °C), anorexia, irritability, malaise, sleeplessness, and headache. Caregivers may attribute these symptoms to teething in children whose primary teeth are erupting, but children who are teething do not have oropharyngeal lesions. The eruption on the oral mucosa begins with red, oedematous marginal gingivae that bleed easily and clusters of small vesicles. The vesicles become yellow after rupture and are surrounded by a

red halo. They coalesce to form large, painful ulcers of the oral and perioral tissues. They bleed easily and may cover with a black crust. The lesions involve the buccal mucosa, tongue, gingiva, hard palate, and pharynx; the lips and perioral skin are affected in approximately two-thirds of cases (fig. 27).

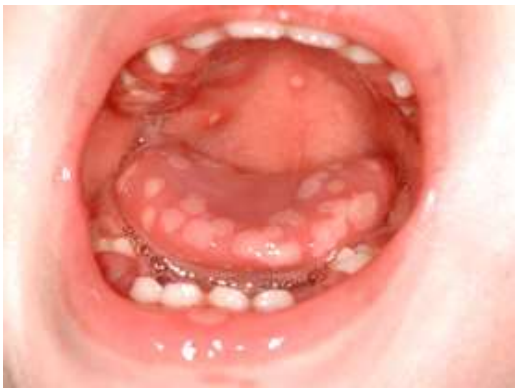

Fig. 27. Herpetic gingivostomatitis

Mild lesions typically heal without scarring in approximately one week, but healing may require 14 to 21 days in severe cases. Associated symptoms and signs may include bad breath, refusal to drink, anorexia, fever, arthralgia, headache, and submandibular or cervical lymphadenitis. Children may require hospitalization for pain control and/or dehydration.

Patients with atopic dermatitis are at risk for developing an HSV-related skin complication called **«eczema herpeticum» (i.e., Kaposi's varicelliform eruption)**, particularly if they are taking immunosuppressive agents for control of their primary dermatologic condition. Examination may reveal skin with punched-out erosions, haemorrhagic crusts and/or vesicular lesions (fig. 28). Eczema herpeticum can spread rapidly, leading to severe morbidity and mortality in the absence of antiviral therapy.

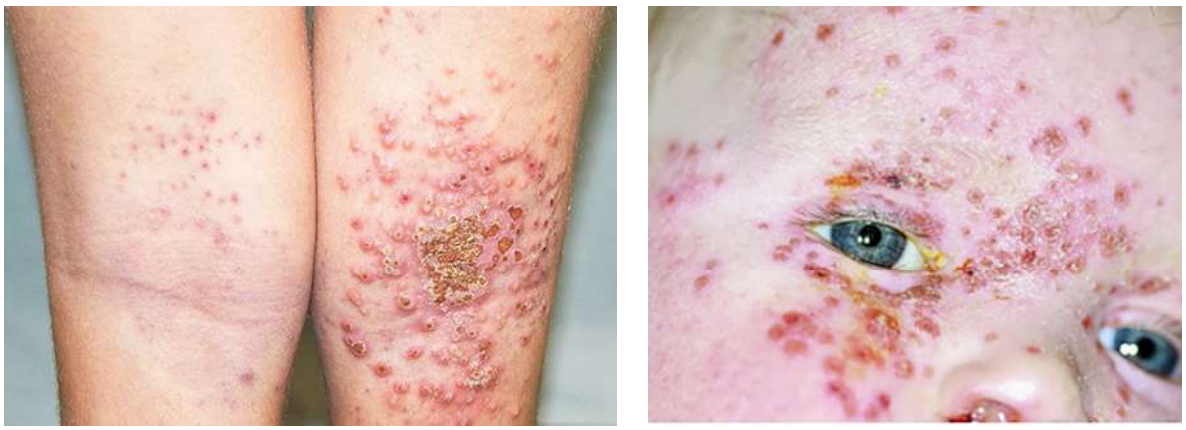

Fig. 28. Eczema herpeticum

Herpes labialis manifests as single or grouped vesicles in the perioral region, usually on the vermilion border of the lips (typically called “cold sores” or “fever blisters”) (fig. 29). Recurrences may be heralded by a prodrome of burning, tingling or itching at the site of an incipient recurrence, identification of which can be useful in instituting antiviral therapy early.

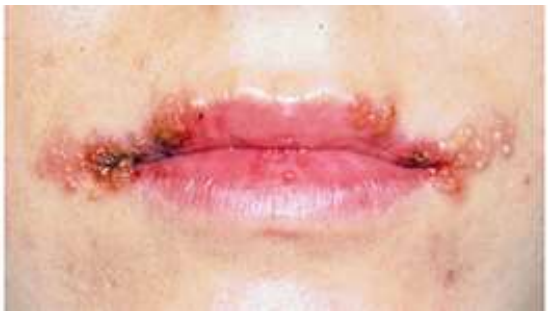

Fig. 29. Herpes labialis

In immunocompromised patients, severe local lesions and, less commonly, disseminated HSV infection with generalized vesicular skin lesions and visceral involvement can occur.

Varicella (chickenpox) is the primary manifestation of VZV infection and is a very common childhood exanthem. After the incubation period of 10 to 21 days, children present with a prodromal state of fever, mild fatigue, and headache, which is followed by a typical exanthem that begins at the hairline and spreads cranial to caudal with a centripetal distribution. Skin lesions are pruritic and rapidly evolve from macules to papules to vesicular and crusted lesions. The characteristic vesicular lesion of varicella shows an erythematous base (dewdrops on a rose petal), and the synchronous manifestation of older and new lesions defines the polymorphous phenotype of varicella exanthem (fig. 30). The rash is usually limited to the trunk and extremities and highly pruritic. In addition, lesions of chickenpox occur in the various mucosa of the body.

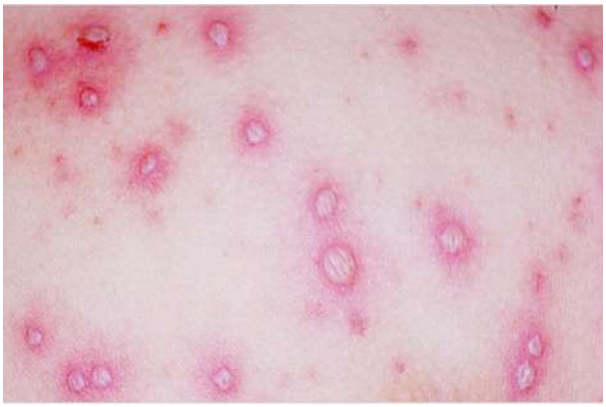

Fig. 30. Chickenpox

Neonatal varicella syndrome occurs in infants born to mothers who have developed a primary varicella from five days before to five days after delivery; this can be fatal in the untreated newborns. Congenital varicella syndrome occurs in 0.4–2 % of children born to mothers infected during the first 28 weeks of gestation.

Herpes zoster (i.e., shingles) represents the reactivation of VZV, which had remained in a latent state in the sensory nerve root ganglia. It typically manifests with pain, burning, tingling, pruritus or hyperesthesia, and 2 to 3 days later erythema and clustered vesicles develop in a sensory dermatomal distribution. There is a predilection for the cervical and sacral dermatomes rash localization in children (fig. 31).

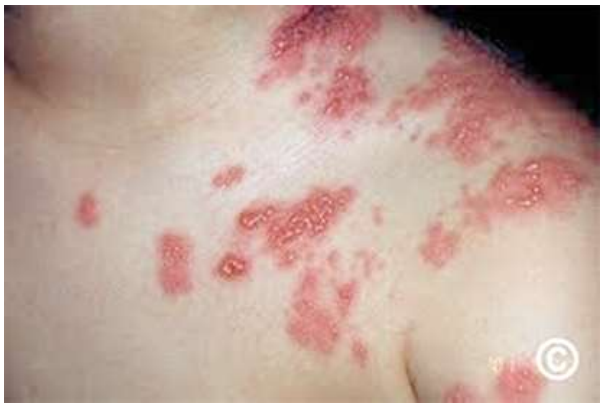

Fig. 31. Herpes zoster

In immunocompromised hosts, distribution may be widespread with visceral involvement in 10 %.

Monkeypox virus infection in infants initially presents with erythematous, macular lesions evolving in a few days to papules, vesicles, and pustules that may involve the whole skin surface including the face, palms, and soles.

Hand, foot and mouth disease is a highly contagious enterovirus illness typically affecting children younger than 5 years of age. Classic HFMD is predominantly localized eruptions limited to the oral cavity with vesicles and painful ulcerations after 1 to 2 days of fever onset, followed by the appearance of typical greyish vesicles with surrounding erythema on the palms and soles (fig. 32). The rash can also develop on the buttocks, trunk, genitalia, face, and limbs.

In most cases, the illness presents with a sudden onset of low-grade fever, loss of appetite, sore throat, cough, abdominal pain, diarrhoea, and general malaise. Arthralgia occurs occasionally. The prodromal period may last for 3 to 4 days and is typically followed by sores appearing on the oral mucosa. Rash on the palms of the hands and soles of the feet can follow within 1 or 2 days. On physical examination, the oropharynx is inflamed, with scattered papules, macules, vesicles, or ulcers on an erythematous base present on the tongue, pharynx, buccal mucosa,

gingiva, and occasionally the lips. If the child presents late, only yellowish ulcerations will be seen, as vesicles tend to rupture quickly. The ulcers are 4 to 8 mm in size and may be sharply marginated. Lesions do not usually involve the soft palate, and generalized ulceration in the mouth is unusual. Erythema and oedema of the tongue may also occur.

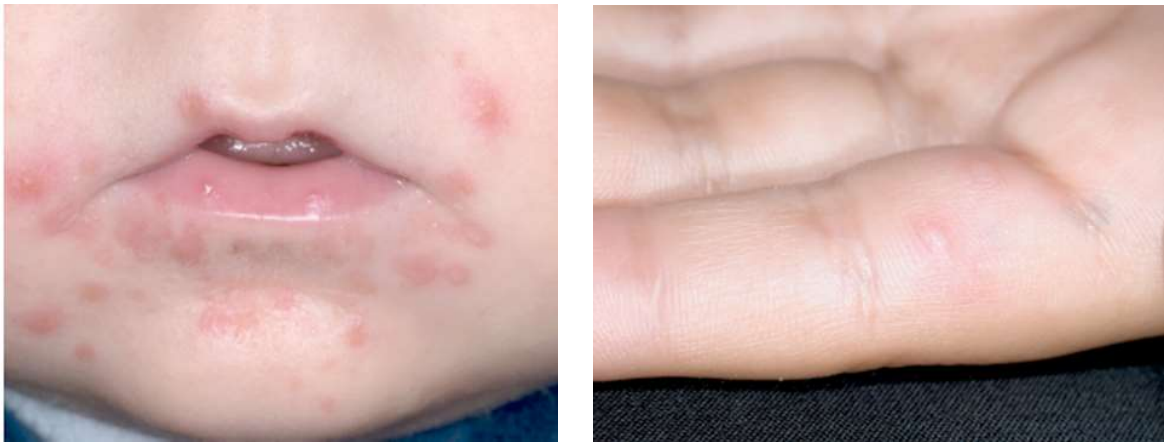

Fig. 32. Hand, foot and mouth disease

There is usually an acral rash involving the palms and soles, with small oval or linear grey-white vesiculopustules. The vesicles are flaccid and thin-walled, with an erythematous halo. They may occasionally be painful or pruritic. They tend to ulcerate and become crusted. Lesions heal within 1 week.

Another clinical syndrome caused by enterovirus infection is **herpangina**. It typically occurs during summer in children aged 3–10 years and is characterized by fever and painful, discrete, grey-white vesicular (usually 3–6) or ulcerative lesions 2–4 mm in diameter on an erythematous base in the posterior oropharynx especially on the soft palate and tonsils (fig. 33). Pain may make the child reluctant to eat. Symptoms resolve in 3–7 days.

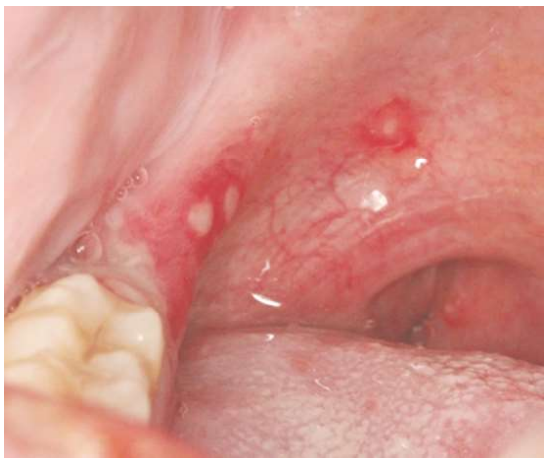

Fig. 33. Herpangina

Impetigo is a common skin infection caused by Staphylococcus aureus and Streptococcus pyogenes. Impetigo occurs in two forms, bullous and non-bullous, and it is highly contagious. Children between 2 and 5 years of age are affected most often. Impetigo can be a primary infection or a secondary infection involving skin compromised by dermatitis or trauma. Factors that predispose to infection include poor hygiene, crowded living conditions, humidity, pre-existing dermatitis, and minor skin trauma.

Non-bullous impetigo is the most common form of the infection, accounting for more than 70 % of cases of impetigo. Lesions of non-bullous impetigo typically form on traumatized skin and are most often located on the exposed skin of the face and extremities. Lesions initially begin as small vesicles or pustules that rupture, forming an adherent, honey-colored crust (fig. 34). Impetigo is associated with minimal pain or erythema, and constitutional symptoms usually are absent. Pruritus, regional lymphadenopathy, and leukocytosis are commonly associated with non-bullous impetigo.

Fig. 34. Impetigo

Bullous impetigo occurs mainly in infants and young children. It is caused by strains of S. aureus, usually from phage group 2 capable of producing an exfoliative toxin that disrupts cell-to-cell adhesion in the superficial epidermis, leading to superficial blister formation. Because the lesions of bullous impetigo are a manifestation of localized toxin production, they develop on intact skin. The flaccid bullae and pustules of this form of impetigo occur beneath the stratum corneum and are easily ruptured, leaving shallow erosions with a collarette of scale. Bullae can be single or clustered; regional lymphadenopathy and systemic symptoms are unusual.

Exfoliative toxin in patients with bullous impetigo may disseminate and cause generalized **Staphylococcal scalded skin syndrome** in immunodeficient states. It is more common in children under 5–6 years (most cases of the disease occur in the first few months of life). The disease onset is acute with a sudden high fever, restlessness, severe and extensive redness of skin (tender erythroderma). The patient's skin, especially in areas of mechanical stress, including flexural areas, buttocks, hands, and feet is red, swollen, and extremely painful that within

1–3 days, with a light pressure large thin-walled blisters will appear, which can be easily torn (positive Nikolsky sign — lateral pressure on unblistered skin in a bullous eruption with resultant shearing off of the epithelium) (fig. 35).

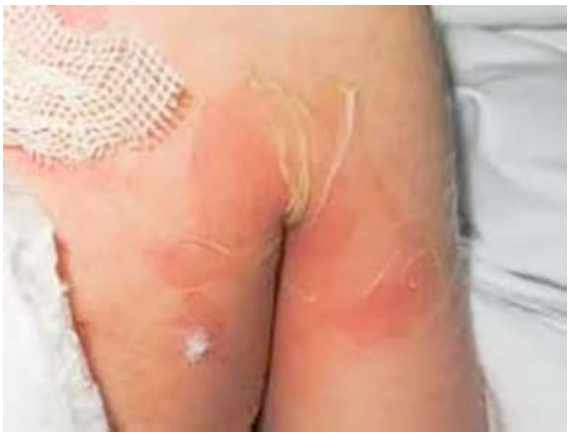

Fig. 35. Staphylococcal scalded skin syndrome

After tear off the blister, a red moisture surface appears that will change to a fine desquamation over the next few days. Because the cleavage plane of the blisters is intraepidermal, scars do not occur.

Congenital syphilis occurs when Treponema pallidum is transmitted from a pregnant woman to her fetus. It should always be included in the differential diagnosis of a newborn with blisters or erosions, especially when present at birth. The incidence has risen markedly in the past several years.

Early manifestations can be quite variable. Infants may be normal at birth and become symptomatic during the first five weeks of life. Haemorrhagic vesicles or bullae and petechiae that start on the palms and soles and spread to the trunk and extremities are nearly pathognomonic of congenital syphilis (fig. 36).

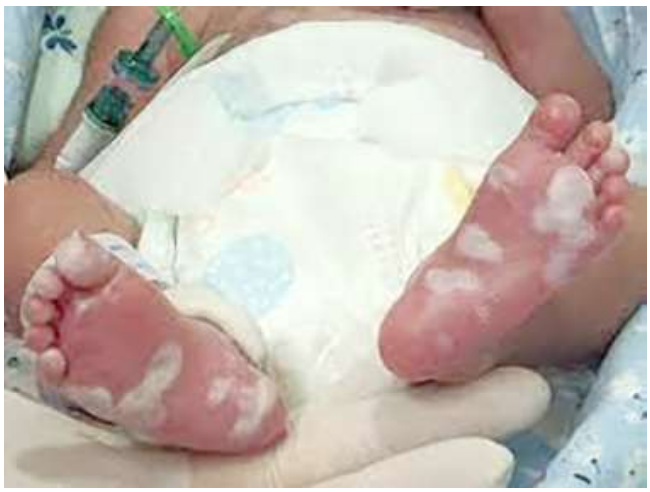

Fig. 36. Congenital syphilis

If ulcerative in nature, they are highly contagious. A more common presentation is a papulosquamous eruption similar to the exanthem of secondary syphilis in adults or a desquamative dermatitis also involving the palms and soles. Other early manifestations include rhinitis, anaemia, thrombocytopenia, lymphadenopathy, hepatomegaly, fever, and poor feeding.

Dermatophyte infections (inflammatory or bullous tinea pedis) are associated with wearing occlusive shoes. Vesicles and bullae present on the medial side of the foot may evolve with superficial erosion with crust, involvement of other areas of foot not usually present.

Epidermolysis bullosa is a rare heterogeneous group of genodermatoses, characterized by skin and mucous membrane fragility, and the formation of blisters in response to minor physical injury. The inheritance of these conditions can be either autosomal dominant or autosomal recessive.

Past history: recurrent episodes of blistering, especially over joints and acral location with minor trauma, family history of similar condition.

Miliaria is a common, transient, vesiculopapular disorder of newborns, especially in warm climates, caused by accumulation of sweat in obstructed eccrine sweat ducts.

Depending on the level of sweat duct obstruction, miliaria presents clinically as ***miliaria crystallina, miliaria rubra (i.e., "heat rash" or "prickly heat"),*** and ***miliaria profunda***. On examination, there are pruritic or asymptomatic papules or vesicles.

Nutritional deficiencies (zinc, biotin, niacin, essential fatty acids) may present as vesicular-bullous dermatitis. Characteristic cutaneous finding is a photosensitive eruption (preferentially involving the face, neck, upper chest, dorsal hands, and extensor forearms), which worsens in spring and summer. With repeated sun exposure, the involved areas become thickened, scaly, and hyperpigmented.

Diabetic bullae (i.e., bullosis diabeticorum) are non-inflammatory, spontaneous, painless blisters that typically occur in acral locations in patients with a longstanding history of diabetes.

Eczematous dermatitis (allergic contact, nummular, and dyshidrotic). *Past history:* personal or family history of atopy, recent exposure to chemicals, personal hygiene products, fabrics, or plant allergens (e.g., poison ivy, poison oak) *On examination*, predominantly localized distribution of vesicles bullae, and papules with surrounding erythematous base, later lesions may be covered by scale or crusting.

Mastocytosis is a heterogeneous group of disorders, characterized by clonal mast cell proliferation in which oedema, urtication, vesicles, and bullae may be seen. Risk of anaphylaxis is elevated in case of mastocytosis due to the increased release of anaphylactic mediators from an excess number of mast cells.

Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis are inflammatory skin conditions that are often drug induced. Twenty per cent of cases are due to exposure to medications, but bacterial and viral triggers

are also common. All are considered variants of a common systemic process of **cutaneous epidermal necrosis** with and without mucosal involvement. Erythema multiforme is the milder form, whereas TEN is the most severe and dangerous.

In most cases, **erythema multiforme** usually occurs in older children and adults. There is burning and itching sensation before the onset of cutaneous lesions. The most important disease-specific lesion is "Target lesion" including a central lesion with discoloration and central necrosis with a normal skin in the margins. There is also a red color change again at the margin of normal skin. The primary central lesion starts as a red maculopapular or urticarial rash and rapidly evolves to central necrosis or may transform to vesiculobullous lesions. The distribution of lesions in the body is symmetrical and occurs at the extensor surface of the upper extremities (the least lesions are seen on face and lower extremities).

The frequency and severity of these lesions are higher in **Stevens-Johnson syndrome**. About 30 % of the body surface area is affected; more lesions are seen on the trunks and limb areas. In these patients, mucosal lesions in more than one mucous membrane also occur. Burning sensation and swelling of the mucous membrane occur before lesion development. Redness, blister, ulcer and/or haemorrhagic crusting on lips, oral mucosa may develop. In a number of cases, fever and chills, pain, burning sensation of mucosa and skin can be seen before eruption of the skin rash.

In cases of **TEN syndrome**, initially painful erythroderma of the skin and then very large, thin-walled blisters occur. Target signs may not be present. Few to 48 hours before skin eruption fever and malaise present. In uncomplicated cases, recovery occurs within 10–14 days.

Thermal burns may result in vesicles and bullae depending on the severity of the burn.

Frostbite refers to soft tissue that is frozen and locally deprived of its blood supply. It presents with various degrees of vesicles and bullae accompanying tissue injury.

Bullous arthropod bite reactions occur in sensitized people as a delayed hypersensitivity immune response.

SELF-CONTROL TASK

1. A 4-year-old child presents with a 3-day history of malaise, fever up to 41.1 °C, cough, coryza, and conjunctivitis. Then he develops the erythematous, maculopapular rash. He is noted to have white pinpoint lesions on the bright red buccal mucosa in the area opposite his lower molars. Which of the following is the most likely diagnosis:

a) erythema infectiosum;
b) rubella;
c) roseola;
d) measles;
e) scarlet fever?

2. A 17-year-old college girl with an extremely sore throat and high fever who develops a rash upon administration of ampicillin. Match the disease with the associated organism:

a) rubivirus;
b) varicella;
c) measles virus;
d) human herpesvirus 6;
e) Epstein-Barr virus.

3. The appearance of an evanescent, erythematous, maculopapular rash following the rapid defervescence of several days of high-grade fever in a 9-month-old boy. Match the disease with the associated organism:

a) rubivirus;
b) varicella;
c) measles virus;
d) human herpesvirus 6.

4. In what case atypical lymphocytes can appear in CBC:

a) scarlet fever;
b) infectious mononucleosis;
c) herpes simplex virus;
d) erythema infectiosum?

5. What disease is accompanied by tonsillitis:

a) measles;
b) rubella;
c) scarlet fever;
d) pseudotuberculosis;
e) varicella;
f) hand, foot, and mouth disease;
g) erythema infectiosum;
h) roseola?

6. What diseases can be accompanied by joint symptoms:

a) measles;
b) rubella;
c) scarlet fever;
d) pseudotuberculosis;
e) erythema infectiosum?

7. A 5-year-old boy presents with a 3-day history of malaise and a mild fever. Within the last 24 h he has complained of a sore mouth and developed vesicles on his hands and feet. He has been well until this illness, and there are no other symptoms. All other family members are well. On examination, he has a temperature of 37.6 °C (99.6 °F) and several small oral ulcers and small oval vesicles with an erythematous base on the palms. What is the aetiology of this condition:

a) measles virus;
b) herpes simplex virus;
c) enterovirus;
d) varicella zoster virus;
e) human herpesvirus 4?

Answer key: ***1*** — d; ***2*** — e; ***3*** — d; ***4*** — b; ***5*** — c; ***6*** — b, d, e; *7* — c.

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Appendix 1

COMMON NON-LIFE-THREATENING DIAGNOSES AND «CAN'T MISS», LIFE-THREATENING DIAGNOSES

Type of disease	Diagnoses
Non-Life-Threatening, Common	Viral exanthema Roseola Parvovirus Coxsackievirus (hand-foot-mouth disease) Varicella Measles Epstein-Barr virus/cytomegalovirus Eczema herpeticum Lyme disease Erythema multiforme Scarlet fever Henoch Schonlein purpura
Life-Threatening diagnoses, «Can't Miss»	Staphylococcal scalded skin syndrome Meningococcal disease Toxic shock syndrome Viral haemorrhagic fevers Stevens-Johnson syndrome/toxic epidermal necrolysis Kawasaki disease Drug reaction with eosinophilia and systemic symptoms Acute rheumatic fever Rocky Mountain spotted fever

Appendix 2

THE CLINICAL PRESENTATIONS AND DIFFERENTIAL DIAGNOSIS OF EXANTHEMATOUS DISEASES

Infection	Duration of prodromal period	Symptoms	Evolution of the rash	Oral enanthems
Measles	3–4 days	Fever, coryza, conjuncti-vitis, cough	Rash: maculopapular, confluent. Extends from the face to the trunk and limbs during 3–4 days and disappears in the same way. Leaves pigmentation for 8–10 days	Koplik spots – white spots on the buccal mucosa before rash
Rubella	1–5 days	Malaise, low-grade fever, coryza, conjuncti-vitis (less in children), lymphadeno-pathy	Starts with a facial rash that spreads to the remainder of the body during 12 h. Concentrated on extensors areas. Duration 3–4 days	Forscheimer's spots – red petechiae on the hard palate
Varicella chickenpox	1–2 days	Rare fever, cough, coryza, sore throat (more common in adults)	Starts as macules and papules and then develops into vesicles that eventually crust over. Lesions at different stages exist at the same time. New elements appear during 5-6 days max	Vesicles which may ulcerate
Erythema infectiosum	2–3 days	Mild fever, malaise (less common in children)	Starts as an erythematous rash on the cheeks that may also progress to include a lacy rash of the trunk and limbs. Indurated erythema in cheeks ('slapped cheeks'). Rash: symmetrical maculopapular rash in the extensor surfaces of upper and lower limbs. Confluent. Duration: 5–10 days (recurrences)	Red macules on palate and buccal mucosa, erythematous tongue

End of the appendix 2

Infection	Duration of prodromal period	Symptoms	Evolution of the rash	Oral enanthems
Roseola infantum (Exanthem Subitum)	3–4 days	High fever which defervesce when rash appears	Starts on the neck and trunk and then spreads to the face and limbs Rash appears when fever disappears: discrete maculopapular. Onset in thorax and trunk, progression to face and limbs. Non-confluent. Duration: 2 days	Nagayama spots – erythematous papules on the soft palate
Scarlet fever	1–2 days	Fever, sore throat, headache, abdominal pain, vomiting	Rash: punctiform, erythematous and rough. It respects the perioral triangle. Onset and predominance in skinfolds. Confluent. Duration: variable, sometimes very brief	Red exudative tonsils, strawberry tongue, palatal petechiae
Enterovirus infections	Variable	Variable	Rash: can cause maculopapular, petechial, and vesicular rashes. Non-itchy and generalized	Herpangina (Coxsackievirus)
Infectious mononucleosis	6–10 days	Prolonged fever.	Rash: may manifest in various forms. More frequent after taking aminopenicillins	Red enlarged tonsils, palatal petechiae
Meningococcal disease	Few hours to 1 day	influenza-like symptoms (fever, headache, myalgia, vomiting, abdominal pain)	The rash in meningococcal disease is typically a non-blanching petechial or purpuric rash (80 % of cases), which evolves from an initial blanching maculopapular rash in 38 % of cases. The rash may be absent, especially in early disease. In severe cases, large ecchymotic areas develop (purpura fulminans) which involve haemorrhage and necrosis in the skin	

CONTENTS

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