virus material. Molluscum contagiosum is spread by contact infection. The virus enters through a break in the skin or a hair follicle, and proliferates in the suprabasal cell layer of the epidermis. When a wart is scratched, the contents adhere to the epidermis and cause autoinfection. Children with atopic dermatitis are most commonly affected. In recent years, the numbers of infections in healthy children at swimming schools, in adults from STDs, and in patients with immunodeficiency have been increasing.

**Pathology**

Molluscum contagiosum is characterized by lobulated, endophytic hyperplasia that produces a circumscribed intracutaneous pseudotumor. The keratinocytes contain very large intracytoplasmic inclusions (molluscum bodies).

**Diagnosis**

Molluscum contagiosum is easily diagnosed by the clinical features. In sudden occurrence of multiple molluscum contagiosum in adults, AIDS involvement is highly suspected.

**Treatment**

Tweezer excision of the lesions is most effective. Cryo-coagulation therapy and application of 40% silver nitrate are also useful. Molluscum contagiosum heals spontaneously in some cases.

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**C. Viral infections whose main symptom is erythematous eruptions**

**1. Measles**

**Outline**

- It is an infectious disease caused by the measles virus. Young children are most frequently affected. It occurs in epidemics with intervals of several years, often during the spring.
- A fever and common-cold-like symptoms occur after an
incubation period of about 2 weeks. When the fever subsides, white macules called Koplik’s spots appear. Fever recurs and eruptions and catarhal symptoms and skin lesion appear on the whole body. The fever subsides rapidly in 3 to 4 days with exfoliation of the eruptions. It heals with pigmentation.

- Otitis media, encephalitis, and subacute sclerosing panencephalitis (SSPE) may occur as complications.
- It is diagnosed by the clinical features or serologically.

**Clinical features**

The clinical features of measles appear after an incubation period of 10 to 14 days. There are prodromal symptoms such as fever, cough and nasal congestion for about 5 days. Grayish-white papules on the buccal mucosa called Koplik’s spots appears as the prodrome subsides, and then enanthema spreads on the forehead, behind the ears, and on sites on the long axis of the body. It is accompanied by high fever. Measles eruptions are characterized by coalesced pink macules and elevated papules (Figs. 23.20 and 23.21). The course of measles is divided into three stages: first (catarrh or prodrome), second (eruption), and third (recovery).

1. **First stage (catarrh)**
   A fever of about 38°C and catarhal symptoms such as nasal discharge, sneezing, eye discharge and cough persist for 3 to 4 days. The respiratory secretions, lacrimal fluid and saliva at this stage are at their most infectious. On the last 1 to 2 days of the catarrhal symptoms, punctate white macules called Koplik’s spots appear on the buccal mucosa and sometimes on the gums at almost the same time as the fever subsides (Fig. 23.22).

2. **Second stage (eruption)**
   After the fever subsides, it recurs (diphasic fever), accompanied by eruptions and aggravation of the catarhal symptoms. It persists for 3 or 4 days. Eruptions first appear behind the ears and cheeks, spreading to the trunk and extremities. Small erythema coalesces and enlarges, forming irregular shapes with a reticular pattern. By this time Koplik’s spots have already disappeared. The measles virus is not found at the lesion; the mechanism is thought to be allergic reaction. Dehydration and various complications often occur from the persistent high fever.

3. **Third stage (recovery)**
   The fever subsides in several days. Healing is with exfoliation of eruptions and pigmentation.

**Complications**

Complications of measles include otitis, pneumonia, encephalitis, myocarditis and subacute sclerosing panencephalitis (SSPE). In atypical measles, vaccination leads to measles with symptoms different from those of usual measles. Atypical measles in recipients of killed measles vaccine (used from 1963 to 1968 in Japan) and immunocompromised persons have been reported.
**Pathogenesis**

The causative viruses are in the family Paramyxoviridae, genus *Morbillivirus*. Infants in the first three months after birth are not infected by the measles virus because of maternal-to-fetal transfer of passive immunity. Infants between the age of 3 months and early childhood are most commonly affected. The measles virus is highly infectious and invades by droplet infection. It proliferates in the epithelial cells of the nasopharynx, resulting in viremia. Subclinical infection rarely occurs; more than 95% of the infected patients show apparent infection. Affected individuals obtain strong permanent immunity.

**Diagnosis**

A decrease of both neutrophils and lymphocytes (leukocytopenia) and an increase of LDH are observed by peripheral blood examination. Serologic assay of antibody responses, viral isolation of respiratory secretions, and PCR are useful for diagnosis.

**Differential diagnosis**

It is differentiated from other viral infection including rubella and exanthema subitum, hemolytic streptococcal infection (scarlet fever), drug eruption, erythema multiforme, Kawasaki disease and sepsis (Fig. 23.23).

**Treatment**

There is no effective treatment for measles. Bed rest, keeping the body warm, and oral antipyretics and antitussives are recommended as symptomatic therapies. Bacterial complications are treated with antibiotics. Human immunoglobulin may be used in severe cases.

**Prevention**

When the route of infection has been defined and no more than 5 days has passed after infection, the onset can be prevented or the symptoms can be mitigated by intramuscular injection of human immunoglobulin. Attenuated live vaccine is used for immunization.

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### 2. Rubella

**Outline**

- Caused by the rubella virus, it is commonly known as German measles or “three-day measles.”
- The main symptoms are eruptions, enlarged lymph nodes (the postauricular lymph node, in particular) and fever.
- Eruptions and fever occur concurrently. Papular erythema accompanied by moderate itching on the face spreads to the whole body surface and does not coalesce. Healing is without scaling or pigmentation.

---

**Fig. 23.23** Differential diagnosis of measles.
Thrombocytopenic purpura and arthritis occur as complications. Arthritis is the only symptom in many adult cases.

Rubella infection in early pregnancy may induce congenital rubella syndrome in fetus. Pregnant women must avoid rubella infection and vaccination.

### Clinical features

Rubella is commonly known as “three-day measles.” The clinical course is shown in **Fig. 23.24**. After a latency of 2 to 3 weeks, the systemic lymph nodes enlarge. Enlargement in the postauricular region and cervical lymph node is particularly noticeable and persists for several weeks. In some cases it begins with eruptions and fever without lymph node enlargement. Several days later, papular erythema accompanied by moderate fever and itching spread on the whole body (**Fig. 23.25**). Unlike measles, the eruptions of rubella are solitary and do not usually coalesce. They disappear without scaling or pigmentation in 3 to 5 days. Petechiae-like enanthema called Forschheimer spots occur in the palate mucosa in about half cases.

### Complication

Encephalitis, meningitis, thrombocytopenic purpura in infancy, and arthritis in adulthood occur as complications.

If a woman is infected in or before her 5th month of pregnancy the newborn may also be affected (congenital rubella syndrome, CRS) (**Table. 23.2**).

### Pathogenesis

The rubella virus, an RNA virus in the family Togaviridae, genus *Rubivirus*, invades the body from the upper respiratory tract by droplet infection or contact infection, proliferates in the regional lymph node, and causes viremia resulting in the onset of rubella. Permanent immunity is obtained after the first infection, although reinfection occurs in rare cases. Most patients are between 5 and 15 years old. Rubella tends to occur in spring and summer epidemics at intervals of 3 to 10 years.

### Laboratory findings, Diagnosis

Leukocytopenia, thrombocytopenia and atypical lymphocytes are found by peripheral blood test. Increased antibody titer is observed by serological assay. Differential diagnosis can be made by detecting IgG and IgM, which is specific to rubella. Cases with moderate symptoms are diagnosed by the clinical course and epidemic circumstances.

### Differential diagnosis

Rubella is differentiated from measles, exanthema subitum and hemolytic streptococcus infection (scarlet fever) (**Fig. 23.23**). Most cases are clinically difficult to diagnose, so serological examination is necessary.

---

**Table 23.2**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incubation period</th>
<th>Lymp node swelling</th>
<th>Papules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (˚C)</td>
<td>38-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days</td>
<td>1 2 3 4 5 6 7 8 9 10 11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Fig. 23.24** The course of rubella

Clinical images are available in hardcopy only.

**Fig. 23.25** Rubella.

a: Erythematous papules on the face and upper chest. b: Erythematous papules on the trunk.

Clinical images are available in hardcopy only.
3. Roseola infantum

Synonym: Exanthema subitum

Outline
- It is caused by human herpes virus (HHV) types 6 and 7. Breast-fed infants are most commonly affected.
- A high fever occurs suddenly and persists for 3 or 4 days. As the fever subsides, measles-like eruptions appear on the whole body. They do not coalesce, but disappear without pigmentation in 2 to 3 days.
- Febrile convulsions may occur as a complication.

Clinical features
After 2-week latency, an acute high fever of 38°C to 39°C occurs and persists for 3 to 4 days. Infected children in most cases appear normal. About when the fever subsides, mild measles-like eruptions occur on the face and trunk. They do not coalesce but disappear in 2 to 3 days without leaving pigmentation (Fig. 23.26). Diarrhea and moderate cough often occur. Seizures may occur during the febrile period in up to 10% of patients. Acute encephalitis and liver dysfunction are complications in rare cases.

Pathogenesis
The causative viruses are thought to be HHV-6 type B and HHV-7. Although HHV-6 is spread by saliva transfer, newborns are not infected because of maternal passive immunity; infants between the ages of 6 months and 3 years are affected.

Diagnosis
Roseola infantum can be diagnosed by the characteristic clinical features. In more than half cases, enlargement and reddening occur in the lymph follicles at the base of the uvula. These findings are helpful for diagnosis.

Treatment
The entire course is between 4 and 6 days, and the prognosis is good. Most cases of roseola infantum are mild and respond well to antipyretics during the febrile period.
Viral Infections

Eruptions, commonly known as fifth or “slapped cheek” disease, are caused by human parvovirus B19.

Flush appears in the cheeks, and papular erythema occurs on the extremities, coalescing to present lacy, reticulated eruptions that predominate in the extremities. These heal without scaling or pigmentation in about 1 week.

Infection in pregnancy may lead to fetal hydrops. If patients with hemolytic anemia are infected, acute pure red cell aplasia occurs, resulting in marked anemia, fetal hydrops or death.

Erythema infectiosum is commonly known as fifth or “slapped cheek” disease. It tends to occur in spring and summer epidemics at intervals of 4 to 6 years. It occurs most frequently in children between 4 and 10 years of age; however, there are also cases in which adults, especially mothers and nurses, are infected by infants and children. Latency is between 2 and 3 weeks. Erythema infectiosum may begin with mild prodromal symptoms. Influenza-like catarrhal symptoms occur in some cases. Erythema that resembles a hand-slap occurs suddenly on both cheeks and disappears in 1 to 4 days (Fig. 23.27). A day or two after the facial lesion manifests, erythematous lesions of about 1 cm in diameter occur on the extensor surfaces of arms and legs. These coalesce gradually and begin to heal at the center, leaving the characteristic lacy, reticulated pattern. When the trunk is involved, no lacey pattern is present. The eruptions disappear without scaling or pigmentation in about 1 week.

When a pregnant woman is infected, prenatal infection occurs in 30% of cases and may cause fatal edema (fetal hydrops) or fatal death. Rapid decrease of erythrocytes (aplastic crisis caused by acute pure red cell aplasia) occurs in cases with hemolytic anemia as an underlying disease, leading to marked anemia.

Pathogenesis

Erythema infectiosum is caused by droplet infection of human parvovirus B19, which is in the Parvovirus genus of DNA viruses. The virus invades the body by respiratory infection and proliferates within erythroblasts of the bone marrow in 4 to 7 days, resulting in viremia. About 2 weeks after infection, production of antibodies begins. At the same time, eruptions appear; involvement of immunocomplex is suggested. Manifest infection occurs in 70% of infant cases and 30% of adult cases.

Laboratory findings

Specific IgG and IgM antibodies are examined by serological assay. In adult cases, antinuclear antibodies are sometimes
detected, which may lead to a misdiagnosis of erythema infectiosum as lupus erythematosus.

**Treatment**

No specific antiviral therapy is available. Intense accessory symptoms are treated symptomatically.

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**5. Gianotti-Crosti disease**

Synonyms: Gianotti disease, Infantile papular acrodermatitis, Papular acrodermatitis of childhood

**Outline**

- Liver dysfunction and eruptions are caused by initial infection of hepatitis B virus. It occurs most frequently in infants.
- Papules appear on the legs, ascending to the arms and face.
- There is a risk that the patient may eventually become a hepatitis B carrier.

**Clinical features**

Gianotti-Crosti disease occurs most frequently in infants between the ages of 6 months and 12 years. After a latency 50 to 180 days, multiple, flat, light pink papules of 3 mm to 4 mm in diameter suddenly appear solitarily on the distal portions of the lower legs. They rapidly ascend to the buttocks, upper arms and face in 3 to 4 days (Fig. 23.28). The trunk is almost never involved. The papules are nearly asymptomatic and disappear spontaneously in about 1 month. Enlargement in the superficial lymph node and liver is present, and hepatic symptoms such as elevated liver enzyme occur; nevertheless, jaundice does not occur.

**Pathogenesis**

Gianotti-Crosti disease is caused by infection of the hepatitis B virus (HBV) in infancy. In most cases there are hepatitis B patients or HBV carriers in the family; the cause is thought to be horizontal transmission.

**Laboratory findings, Diagnosis**

Increases in serum AST, ALT, LDH and ALP are observed from hepatic symptoms. HBs antigens are positive. The eruptions disappear in about 1 month, and HBs antigens disappear in several months. Gianotti-Crosti disease is relatively easily diagnosed by the clinical features and enlargement of the lymph nodes and liver. HBs antigens are observed by blood test; if they are negative, there is high possibility of Gianotti-Crosti syndrome (described below).

**Treatment, Course of disease**

When HBs antigens persist after the eruptions disappear, the
patient may progress to become a carrier. About half of patients under the age of 1 become carriers. Prevention of such progression is of primary importance. Interferon, anti-HBV antibody hyperimmune globulin, and glycyrrhizinate are used.

**Gianotti-Crosti syndrome**

The eruptions caused by Gianotti-Crosti syndrome closely resemble those of Gianotti-Crosti disease; however, the former are accompanied by intense itching and often occur on the trunk (Figs. 23.29-1 and 23.29-2). The main causative viruses are cytomegalovirus, Epstein-Barr virus, and coxsackievirus. HBs antigen is negative. There are no findings of liver dysfunction.

**6. Infectious mononucleosis**

**Outline**

- It is caused by infection of Epstein-Barr virus. It occurs most frequently in puberty.
- The main symptoms are high fever, pharyngeal pain, and swelling in the cervical lymph nodes. Rubella-like and measles-like eruptions and erythema multiforme appear in 30% of cases.
- Symptomatic therapy is the main treatment. Penicillin-containing drugs and aspirin are contraindicated.

**Clinical features**

The latency of infectious mononucleosis is 1 to 2 months. After prodromes such as headache and generalized fatigue that persist for several days, a high fever (higher than 39°C) and intense pharyngeal pain occur. Eruptions appear 4 to 10 days after the onset in about 30% of cases (Figs. 23.30-1 and 23.30-2). The eruptions may present as rubella-like eruptions, measles-like eruptions, or erythema multiforme. Drugs (penicillin in particular) induce hypersensitive reaction and aggravate the eruptions. Marked swelling is seen in the whole body, particularly in the cervical lymph nodes. There is tenderness but no spontaneous pain. Splenomegaly accompanied by hepatic dysfunction often occurs. The fever subsides in 7 to 10 days, after which symptoms gradually subside. Thrombocytopenia, hemolytic anemia, encephalomyelitis and Guillain-Barre syndrome occur as complications.

**Pathogenesis, Epidemiology**

Infectious mononucleosis is caused by infection of Epstein-Barr virus (EBV). Permanent immunity is obtained from the first infection. EBV is always present in the oral cavity, and it easily spreads orally or through inhalation. The virus invades the body, proliferates in the epithelial cells of the pharyngeal mucosa, and travels to the regional lymph node. It immortalizes B cells by
C. Viral infections whose main symptom is erythematous eruptions

latently infecting them through CD21 on their surface. The pathogenesis is thought to be reactivation of B cells against the organic immune mechanism, which induces inflammation. In Japan more than 80% of infants experience EBV exposure through mother-to-child infection, but they are subclinical. Conversely, when the first infection occurs in adolescence, apparent infection takes place as infectious mononucleosis. Patients are often infected by the opposite sex; infectious mononucleosis is commonly called kissing disease. In recent years, antibody prevalence has decreased, and the incidence of infectious mononucleosis is increasing. It occurs most frequently in adolescents between the ages of 14 and 18, regardless of the season.

**Laboratory findings**

The leukocyte count approaches 10,000 per microliter, and more than half of it is mononuclear cells, of which 10% are particularly large atypical lymphocytes. These cells are not B cell but CD8+T cells that are activated to exclude infected cells. Increased serum AST, ALT and ALP titers resulting from liver dysfunction and antibodies produced by B cells lead to elevated levels of polyclonal human immunoglobulin. Paul-Bunnel test, which measures an antibody reaction in blood to sheep erythrocytes, used to be helpful for diagnosis. However, because of the more diagnostically valuable measurement of viral antibody titer (Fig. 23.31), it is no longer used.

**Diagnosis**

Infectious mononucleosis is diagnosed by the clinical features, which include marked lymph node enlargement, findings of the blood, and serological findings (Table 23.3).

**Treatment**

There are no specific treatments for infectious mononucleosis, other than bed rest and symptomatic therapies. Drugs containing aspirin or penicillin are contraindicated: Aspirin may cause Reye’s syndrome and penicillin may induce hypersensitive reaction as severe eruptions.

**Table 23.3 Diagnostic criteria for infectious mononucleosis.**

<table>
<thead>
<tr>
<th>3 major symptoms</th>
<th>Remittent fever swelling of systemic lymph nodes, elevated atypical lymphocytes in the peripheral blood</th>
</tr>
</thead>
</table>
| Hematological findings | Rate of lymphocytes + monocytes >50% (typically >60%)  
Rate of atypical lymphocytes >10% (typically >20%) |
| Liver function findings | Increases in AST, ALT, and LDH Abnormality of TTT and ZTT |
| Serological findings | EB virus antibody titer rise  
1. Anti-VCA IgG antibody 1: >160  
2. Anti-VCA IgM antibody 1: >10 or anti-EA-DR IgG antibody 1: >10  
3. Anti-EBNA antibody negative in acute phase  
All criteria (1.-3.) are generally met. In some cases, 3. and either 1. or 2. are met. |
| Auxiliary findings | Palpbral edema, palate ecchymosis, pharyngitis, fever unresponsive to antimicrobials for 5 days or more (young person), liver pain by tapotement, and splenohepatomegalies |

**Fig. 23.30-2 Infectious mononucleosis.**

c: Lesion on the trunk.

**Fig. 23.31 Changes of antibody titer related to EBV, and staging of infectious mononucleosis.**
