Legionellosis

Pathogen

- *Legionella pneumophila* is an important cause of both nosocomial and community-acquired pneumonia (CAP) and must be considered a possible causative pathogen in any patient who presents with pneumonia.
- The *Legionella* bacterium was first identified in the summer of 1976 during the 58th annual convention of the American Legion, which was held at the Bellevue-Stratford Hotel in Philadelphia.
- Infection was presumed to be spread by contamination of the water in the hotel's air conditioning system.
- The presentation ranged from mild flulike symptoms to multisystem organ failure. Of the 182 people infected, 29 died.
- A bacterium that would later be named *L pneumophila* was isolated from different organ tissues of guinea pigs inoculated with lung tissue samples from 4 individuals who died.
- Although this pathogen was not identified until 1976, retrospective analysis suggests that *L pneumophila* may have been responsible for previous pneumonia epidemics in Philadelphia; Washington, DC; and Minnesota. *L pneumophila* was identified in a clinical specimen dating to 1943.

Pathophysiology

- The *Legionella* bacterium is a small, aerobic, waterborne, gram-negative, unencapsulated bacillus that is nonmotile, catalase-positive, and weakly oxidase-positive. *Legionella* is a fastidious organism and does not grow anaerobically or on standard media. Buffered charcoal yeast extract (CYE) agar is the primary medium used for isolation of the bacterium.
- The Legionellaceae family consists of more than 42 species constituting 64 serogroups.
- *L pneumophila* is the most common species, causing up to 90% of the cases of legionellosis, followed by *Legionella micdadei* (otherwise known as the Pittsburgh pneumonia agent), *Legionella bozemanii, Legionella dumoffii,* and *Legionella longbeachae.*
- Fifteen serogroups of *L pneumophila* have been identified, with serogroups 1, 4, and 6 being the primary causes of human disease. Serogroup 1 is thought to be responsible for 80% of the reported cases of legionellosis caused by *L pneumophila.*

Pathophysiology

- *Legionella* species are obligate or facultative intracellular parasites. Water is the major environmental reservoir for *Legionella.*
- The bacterium can infect and replicate within protozoa such as *Acanthamoeba* and *Hartmannella* species, which are free-living amoebae found in both natural and manufactured water systems.
- The *Legionella* species within the amebic cells can avoid the endosomal-lysosomal pathway and can replicate within the phagosome.
- *Legionella* can survive and grow in the amebic cells, thereby enabling the organism to persist in nature.
- *Legionella* species infect human macrophages and monocytes, and intracellular replication of the bacterium is observed within these cells in the alveoli.
- The intracellular infections of protozoa and macrophages have many similarities.

Transmission

- Transmission is thought to occur via inhalation of aerosolized mist from water sources (eg, whirlpools, showers, cooling towers) contaminated with either the bacterium or amebic cells infected with the bacterium.
- Direct inhalation is the most likely method of transmission, with aerosol-generating systems playing a crucial role.
- Person-to-person transmission has not been documented.
- The highest incidence occurs during the warmer months, when air-conditioning systems are used more frequently.
- Nosocomial acquisition likely occurs via aspiration, respiratory therapy equipment, or contaminated water. In addition, transmission has been linked to the use of humidifiers, nebulizers, and items that were rinsed with contaminated tap water.

History

- *L pneumophila* causes 2 distinct disease entities. Legionnaires disease (LD) is characterized by pneumonia. Pontiac fever is a milder illness than LD and is not characterized by pneumonia; Pontiac fever manifests as fever and myalgias that resolve without treatment.

- Legionnaires disease
  - The incubation period ranges from 2-10 days.
  - Patients who develop legionellae infection and who have been hospitalized continuously for 10 or more days before the onset of illness are classified as having definite nosocomial LD. Patients with laboratory-confirmed infection that develops 2-9 days after hospitalization are classified as having possible nosocomial LD.
  - Nosocomial LD occurs in clusters.
  - Individuals with LD can present with a broad spectrum of symptoms.

Symptoms of legionnaires disease

- Fever greater than 40 ° C (>102 ° F)
- Chills
- Cough - Dry or productive; hemoptysis rare
- Pleuritic or nonpleuritic chest pain
- Neurologic symptoms
  - Headache
  - Lethargy
  - Encephalopathy
  - Mental status changes - The most common neurologic symptom
- GI symptoms
  - Diarrhea - Watery, not bloody
  - Nausea, vomiting, and abdominal pain
- Myalgias

Physical

- Manifestations of LD may include the following:
  - Mental status changes
  - Fever greater than 40°C (range, 38.8-40.5°C)
  - Hypotension
  - Relative bradycardia in all (excluding patients with pacemakers or arrhythmias or those receiving beta-blockers, diltiazem, or verapamil)
  - Tachypnea
  - Localized rales
  - Depressed mental status or agitation
- Extrapulmonary manifestations
  - In addition to relative bradycardia, cardiac manifestations are common findings and include myocarditis, pericarditis, and prosthetic valve endocarditis.
  - Pancreatitis
  - Peritonitis
  - Acute renal failure

Laboratory Studies

- While pneumonias caused by numerous pathogens share similar laboratory findings, hyponatremia (sodium <130 mEq/L) secondary to the syndrome of inappropriate antidiuretic hormone is more common in legionnaires disease (LD) than in pneumonias secondary to other pathogens; however, this is not specific for LD.
- Additional laboratory findings in LD and in pneumonias due to other causes include the following:
  - Elevated liver enzyme levels
  - Increased creatine phosphokinase levels
  - Increased creatine phosphokinase (CPK) levels
  - Increased C-reactive protein levels (>30 mg/L)
  - Hypophosphatemia (specific to LD excluding other causes of hypophosphatemia)4
  - Microscopic hematuria
  - Proteinuria (40%)

Serology/Diagnosis

- The most widely used tests include the immunofluorescent antibody (IFA) and enzyme-linked immunosorbent assay (ELISA). A single increased antibody titer confirms LD if the IFA titer is greater than or equal to 1:256.
- While LD serologic tests are the most readily available, they require a 4-fold increase in antibody titer to 1:128 or greater, which takes 4-8 weeks. Paired measurements from both the acute and convalescent periods should be obtained, since an antibody response may not be apparent for up to 3 months. Of note, antibody levels do not increase in approximately one third of patients with LD.
- Urinary antigen test
  - The *Legionella* lipopolysaccharide antigen is detected with ELISA, radioimmunoassay (RIA), and the latex agglutination test. The *Legionella* lipopolysaccharide antigen becomes detectable in 80% of patients on days 1-3 of clinical illness.
  - The urinary antigen assay can be used to detect only *L pneumophila* (serogroup 1).5
  - The advantages of this test include rapidity and simplicity. In addition, the relative ease of obtaining a urine sample compared with obtaining sputum specimens and the persistence of antigen secretion in patients who are on antibiotic therapy increase the usefulness of the urine antigen detection method.5
  - The urinary antigen result can remain positive for months after the acute episode has resolved.5
- Amplification with polymerase chain reaction
  - Polymerase chain reaction (PCR) of urine, serum, and bronchiolar lavage fluid is very specific for the detection of legionellae, but the sensitivity is not greater than that of culture.
  - The primary benefit of this procedure, like IFA titers, is that it can be used to detect infections caused by legionellae other than *L pneumophila* serogroup 1.6

Treatment

- Historically, erythromycin was used for *L pneumophila* infection, but doxycycline, azithromycin, macrolides, and quinolones are more active against legionnaires disease (LD) than erythromycin.
- The fluoroquinolones, doxycycline, telithromycin, and azithromycin are superior because of their activity and pharmacokinetic properties (eg, better bioavailability, better penetration into macrophages, longer half-life).
- For severe disease, a fluoroquinolone is recommended.
- Severe disease is defined by respiratory failure, bilateral pneumonia, rapidly worsening pulmonary infiltrates, or the presence of at least 2 of the following 3 characteristics:
  - Blood urea nitrogen greater than or equal to 30 mg/dL
  - Diastolic blood pressure lower than 60 mm Hg
  - Respiratory rate greater than 30/min
- With doxycycline or fluoroquinolones, rifampin does not need to be added in severely ill patients.
- Most healthy hosts exhibit clinical response to treatment within 3-5 days.

Infectious mononucleosis

Infectious mononucleosis

- It was first described simultaneously by Filatov and Pfeiffer at the end of the 19-th century characterized by malaise, fever, hepatosplenomegaly, lymphadenopathy and abdominal discomfort.
- The illness came to be known as glandular fever
- The discovery of the virus was made in 1964 by Epstein and his coworkers (Barr and Achong), who discovered the virus particles in a tissue specimen obtained from Burkitt's lymphoma from Africa

Overview

- Infectious mononucleosis (often called "mono") is a common viral infection that causes fever, sore throat, and enlarged lymph nodes. The most common complaint is a sore throat. Mono is most commonly caused by the Epstein-Barr virus (EBV). Mono is most frequently diagnosed in teenagers and young adults.
- The illness generally goes away without medical help. However, it may last from weeks to months. Treatment is mainly to ease symptoms, usually at home, with plenty of rest and fluids.
- By adulthood, 90%-95% of men and women have been infected with EBV. Mono most often occurs in people 5-25 years of age and is highly contagious. Not surprisingly, 1%-3% of college students contract mono each year. Infection spreads through exposure to body fluids containing the virus. It is most often transmitted via saliva (hence the name "kissing disease"). However, mono can also be spread through blood and genital secretions.
- Serious complications rarely occur.

Clinical types

- Depending on the dominance of the symptoms:
  - Pharyngeal
  - Glandular
  - Hepatic
  - Typhoid

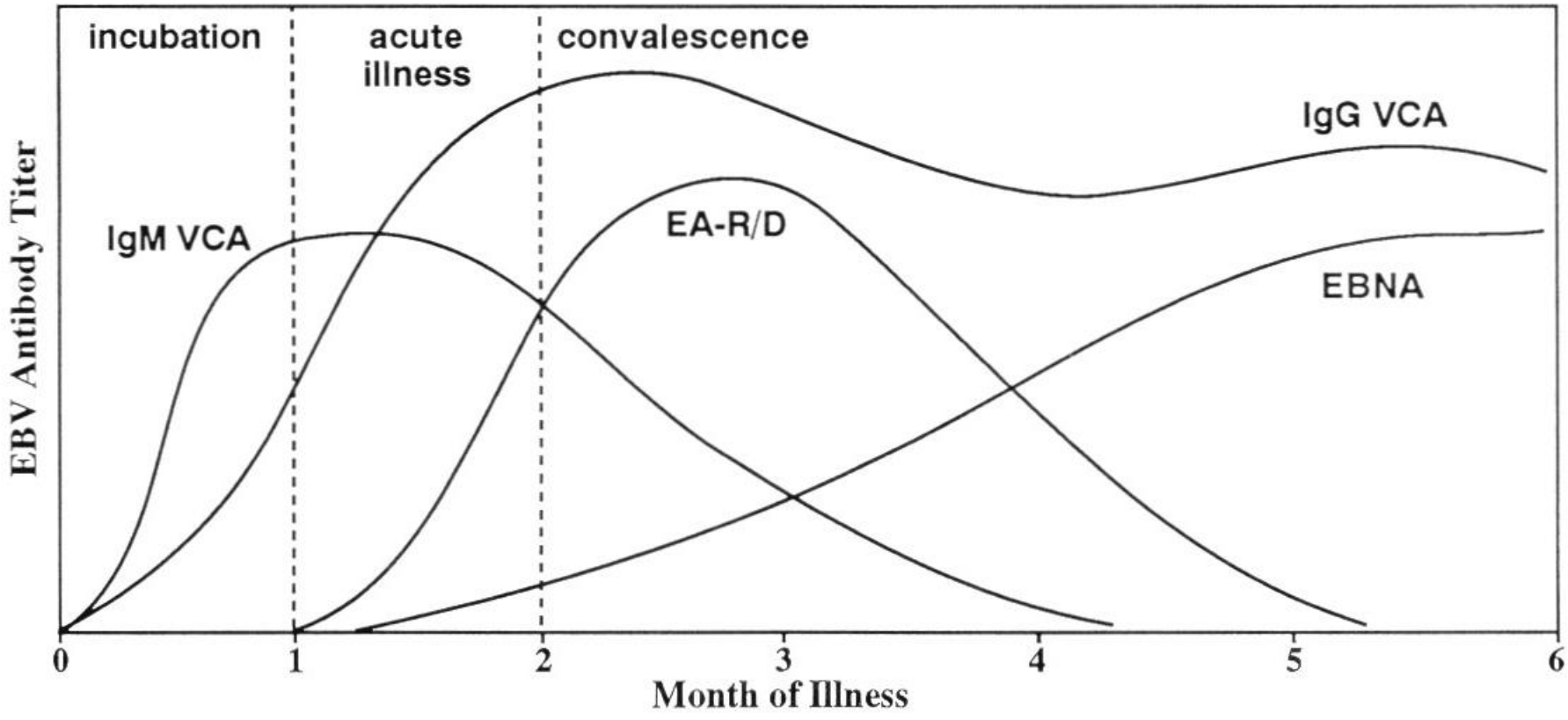
Pathophysiology

- EBV is transmitted via intimate contact with body secretions, primarily oropharyngeal secretions. EBV infects the B cells in the oropharyngeal epithelium. The organism may also be shed from the uterine cervix, implicating the role of genital transmission in some cases. On rare occasion, EBV is spread via blood transfusion.
- Circulating B cells spread the infection throughout the entire reticular endothelial system (RES), ie, liver, spleen, and peripheral lymph nodes. EBV infection of B lymphocytes results in a humoral and cellular response to the virus. The humoral immune response directed against EBV structural proteins is the basis for the test used to diagnose EBV infectious mononucleosis. However, the T-lymphocyte response is essential in the control of EBV infection; natural killer (NK) cells and predominantly $CD8^+$ cytotoxic T cells control proliferating B lymphocytes infected with EBV.

Pathophysiology

- The T-lymphocyte cellular response is critical in determining the clinical expression of EBV viral infection. A rapid and efficient T-cell response results in control of the primary EBV infection and lifelong suppression of EBV.
- Ineffective T-cell response may result in excessive and uncontrolled B-cell proliferation, resulting in B-lymphocyte malignancies (eg, B-cell lymphomas).
- The immune response to EBV infection is fever, which occurs because of cytokine release consequent to B-lymphocyte invasion by EBV.
- Lymphocytosis observed in the RES is caused by a proliferation of EBV-infected B lymphocytes.
- Pharyngitis observed in EBV infectious mononucleosis is caused by the proliferation of EBV-infected B lymphocytes in the lymphatic tissue of the oropharynx.

Serological response



Frequency

- EBV infectious mononucleosis is a common cause of viral pharyngitis in patients of all ages, but it is particularly frequent in young adults.
- In the United States, approximately 50% of the population seroconverts before age 5 years, with much of the rest seroconverting in adolescence or young adulthood.
- Approximately 12% of susceptible college-aged young adults convert each year, half of whom develop acute infectious mononucleosis.

Mortality/Morbidity

- Patients with EBV infection who present clinically with infectious mononucleosis invariably experience accompanying fatigue. Fatigue may be profound initially but usually resolves gradually in 3 months. Some patients experience prolonged fatigue and, after initial recovery, enter a state of prolonged fatigue without the features of infectious mononucleosis.
- Mortality and morbidity rates due to uncomplicated primary EBV infectious mononucleosis are low. The rare cases of attributed mortality are usually related to spontaneous splenic rupture. Splenic rupture may be the initial presentation of EBV mononucleosis.
- Most cases of EBV infectious mononucleosis are subclinical, and the only manifestation of EBV infection is a serological response to EBV surface proteins discovered with EBV serological tests. Airway obstruction and central nervous system (CNS) mononucleosis are also responsible for increased morbidity in infectious mononucleosis. Selective immunodeficiency to EBV, which occurs in persons with X-linked lymphoproliferative syndrome, may result in severe, prolonged, or even fatal infectious mononucleosis.

History

- Most patients with Epstein-Barr virus (EBV) infectious mononucleosis are asymptomatic and, therefore, have few if any symptoms. Most adults (approximately 90%) show serological evidence of previous EBV infection.
- The incubation period of EBV infectious mononucleosis is 1-2 months. Many patients cannot recall close contact with individuals with pharyngitis. Virtually all patients with EBV infectious mononucleosis report fatigue and prolonged malaise. A sore throat is second only to fatigue and malaise as a presenting symptom.
- Fever is usually present and is low grade, but chills are relatively uncommon. Arthralgias and myalgias occur but are less common than in other viral infectious diseases.
- Nausea and anorexia, without vomiting, are common symptoms.

History

- Various other symptoms have been described in patients with EBV infectious mononucleosis, including cough, ocular muscle pain, chest pain, and photophobia.Importantly, patients without CNS involvement experience no cognitive difficulties.
- CMV infectious mononucleosis rarely involves the CNS.Myalgias, which are uncommon, are rarely (if ever) severe.

Physical

- Physical findings in infectious mononucleosis should be viewed in terms of frequency distribution and time course after clinical presentation.
- Early signs include fever, lymphadenopathy, pharyngitis, rash, and/or periorbital edema. Relative bradycardia has been described in some patients with EBV mononucleosis, but it is not a constant finding.
- Later physical findings include hepatomegaly, palatal petechiae, jaundice, uvular edema, splenomegaly, and, rarely (1-2%), findings associated with splenic rupture.
- CNS findings associated with EBV mononucleosis are rare but usually occur later in the course of the illness.

Physical

- Splenic tenderness may be present in patients with splenomegaly.
- Pulmonary involvement is not a feature of EBV infectious mononucleosis.
- The classic presentation of EBV infectious mononucleosis in children and young adults consists of the triad of fever, pharyngitis, and lymphadenopathy.
- Older adults and elderly patients with EBV infectious mononucleosis often have few signs and symptoms referable to the oropharynx and have little or no adenopathy.
- Elderly patients with EBV mononucleosis present clinically as having anicteric viral hepatitis.
- Predictably, jaundice develops in less than 10% of young adults with EBV infectious mononucleosis, but jaundice may occur in as many as 30% of affected elderly individuals.

Physical

- The pharyngitis due to EBV infectious mononucleosis may be exudative or nonexudative.
- Exudative pharyngitis is commonly confused with group A streptococcal pharyngitis, which is complicated further by the fact that approximately 30% of patients with EBV infectious mononucleosis have group A streptococcal carriage of the oropharynx.
- The unwary physician may incorrectly conclude that a throat culture or rapid test positive for group A streptococci in a patient with infectious mononucleosis represents streptococcal pharyngitis.
- Nonexudative pharyngitis with or without tonsillar enlargement is common in patients with EBV infectious mononucleosis and resembles viral pharyngitis.
- Patients with either exudative or nonexudative EBV infectious mononucleosis are commonly colonized by group A streptococci.

Physical

- Tonsillar enlargement is common, and massive tonsillar enlargement may be observed.
- The term kissing tonsils is used to describe extreme enlargement of both tonsils in patients with EBV infectious mononucleosis.
- Extreme tonsillar enlargement may result in airway obstruction.
- Palatal petechiae of the posterior oropharynx distinguish infectious mononucleosis from other causes of viral pharyngitis but do not distinguish it from group A streptococcal pharyngitis, in which palatal petechiae may occur.

Physical

- Uvular edema is an uncommon finding in infectious mononucleosis, but, if present, it is a helpful sign in distinguishing EBV infectious mononucleosis from other causes of viral pharyngitis or from group A streptococcal pharyngitis.
- Early in the course of EBV infectious mononucleosis, patients may present with a maculopapular generalized rash. The rash is faint and evanescent and rapidly disappears. It is nonpruritic. This is a marked contrast to patients mistakenly diagnosed with streptococcal pharyngitis who have been administered ampicillin or amoxicillin and then develop a maculopapular rash as a drug reaction. Drug-induced rash is usually pruritic and is prolonged, in contrast to the viral rash of EBV infectious mononucleosis.
- Patients with EBV infectious mononucleosis who experience drug reactions to beta-lactams are not allergic to these medications. Administration of beta-lactams after resolution of the infection does not result in drug fevers or rashes.

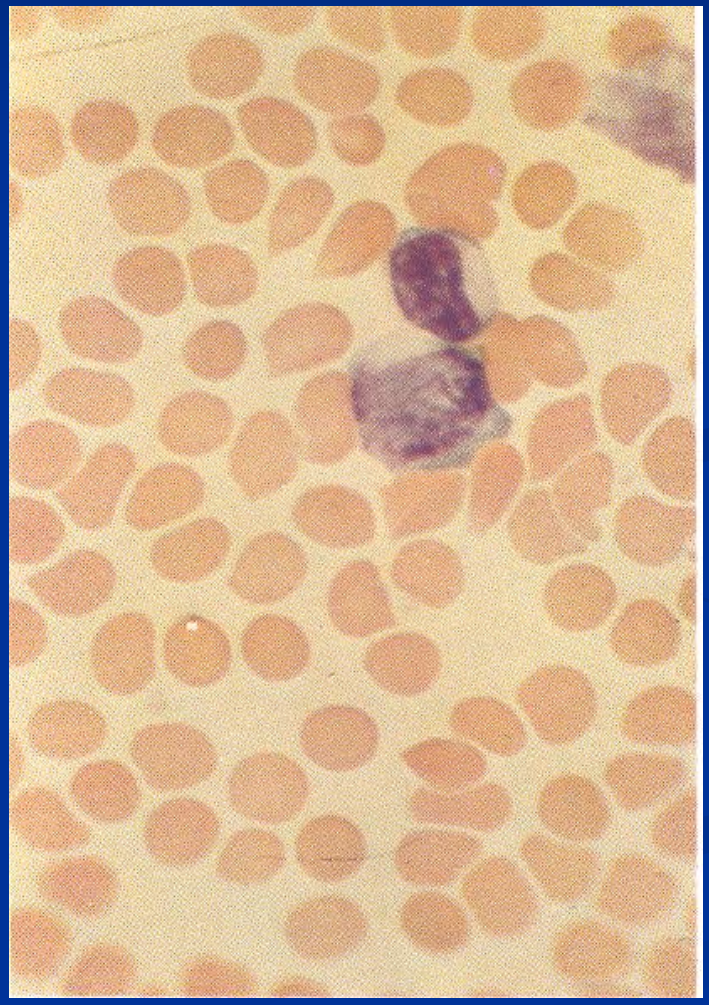
Physical

- Splenomegaly is a late finding in EBV infectious mononucleosis.
- Splenic enlargement returns to normal or near normal usually within 3 weeks after the clinical presentation.In rare cases, EBV infectious mononucleosis results in various unusual clinical manifestations, including encephalitis, pancreatitis, acalculous cholecystitis, myocarditis, mesenteric adenitis, myositis, and glomerular nephritis.
- Neurologic syndromes due to EBV infectious mononucleosis include optic neuritis, transverse myelitis, aseptic meningitis, encephalitis, meningoencephalitis, cranial nerve (CN) palsies (particularly CN VII), and Guillain-Barré syndrome.

Laboratory

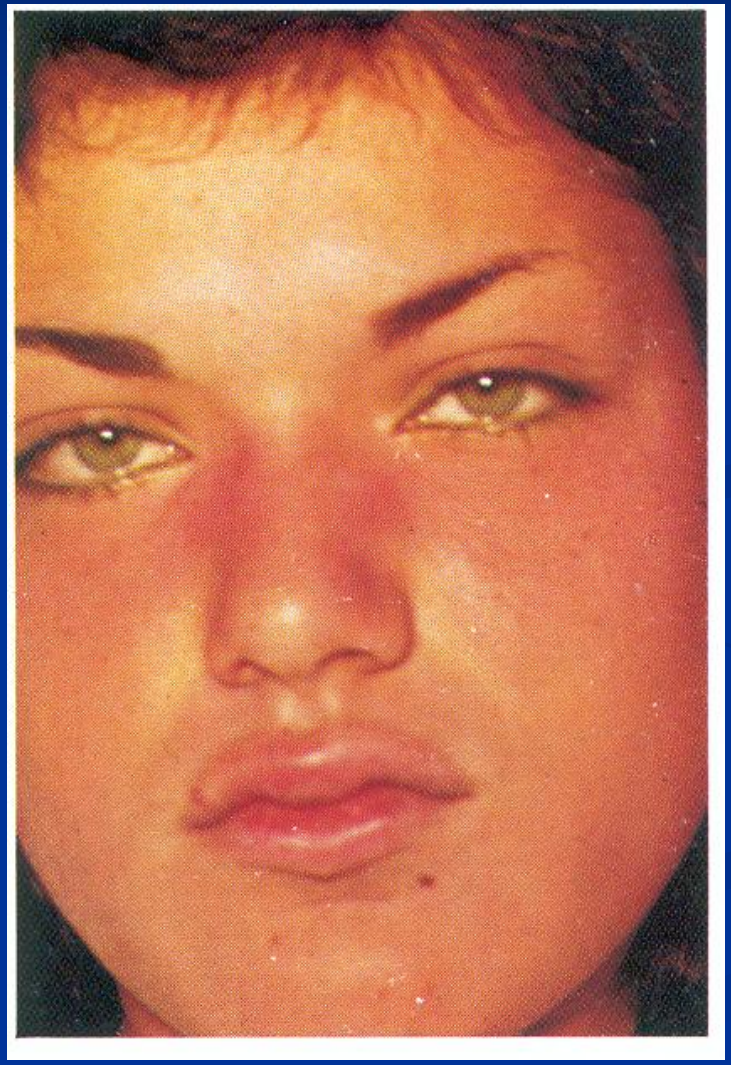
- Although EBV-induced antibodies to RBC membranes may occur, clinical anemia is uncommon with EBV infectious mononucleosis.
- Leukocytosis, rather than leukopenia, is the rule in infectious mononucleosis.
- Blood smear shows the appearance of atypical mononuclear cells
- Heterophyl antibodies are present (Monosticon)

Mononuclear cells

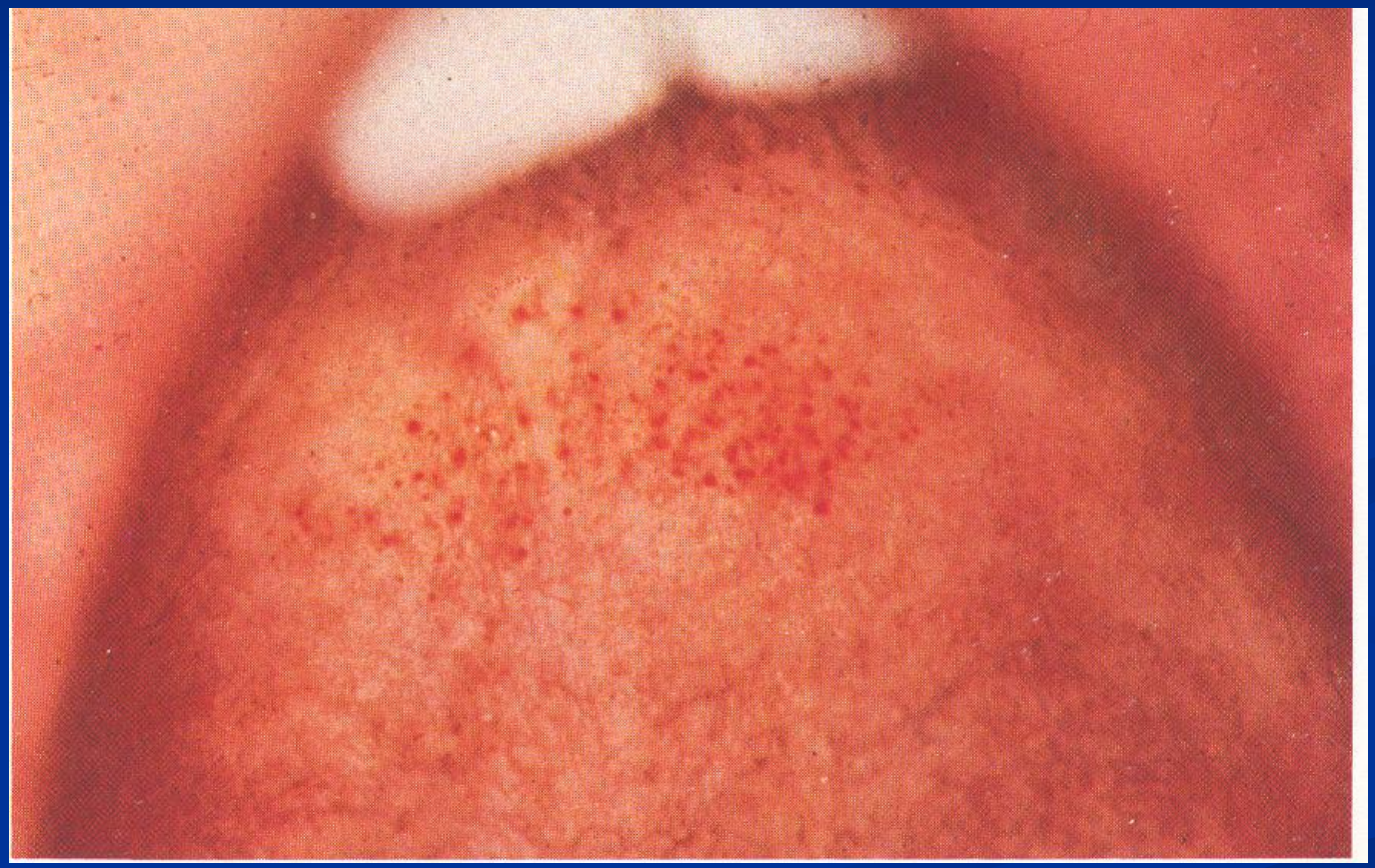


Clinical parameters		EBV	Cytomegalovirus	Toxoplasmosis	Viral hepatitis
Symptoms	Fatigue	+++	+	+/-	+
	Malaise	++	+	-	+
	Mild sore throat	+	+	+/-	-
	Early maculopapular rash	+/-	-	-	-
	Early bilateral upper eyelid edema	+/-	-	-	-
	Unilateral localized adenopathy	-	-	+	-
Signs	Bilateral posterior cervical adenopathy	+	+	-	+/-
	Tender hepatomegaly	+/-	+/-	-	+/-
	Splenomegaly	+	+/-	+/-	-
	WBC count	N/-	N/-	N	_
Laboratory abnormalities	Elevated SGOT/SGPT	++	+	+/-	+++
	Atypical lympocytes (above 10%)	+	+	-	-
	Thrombocytopenia	+/-	+/-	-	+/-
	Elevated IgM CMV titer	-	+	-	-
	Elevated IgM toxoplasmosis titer	-	-	+	-
	Elevated hepatitis IgM titer	-	-	-	+

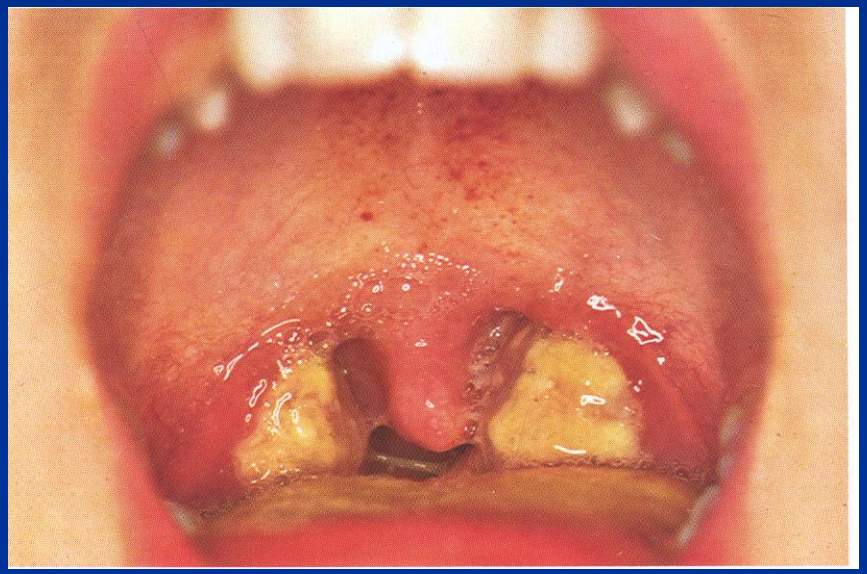
Characteristic face of infectious mononucleosis

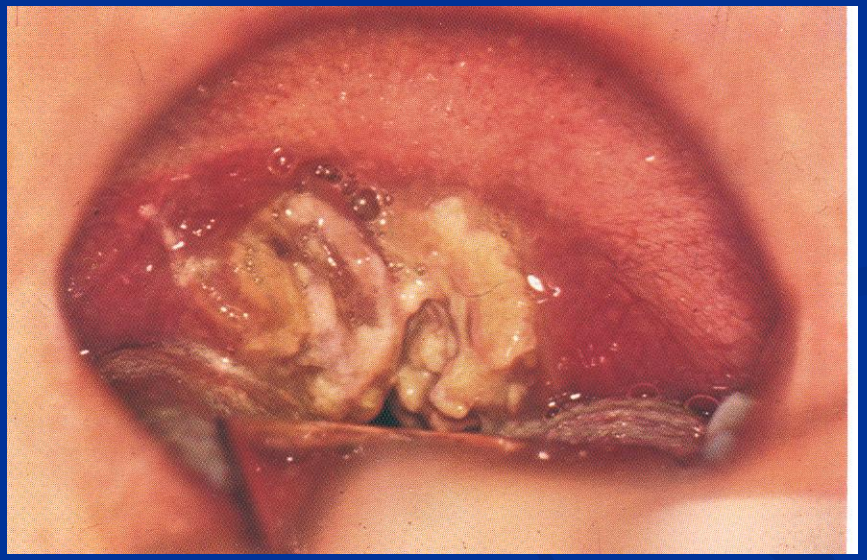


Petechiae on the soft palate

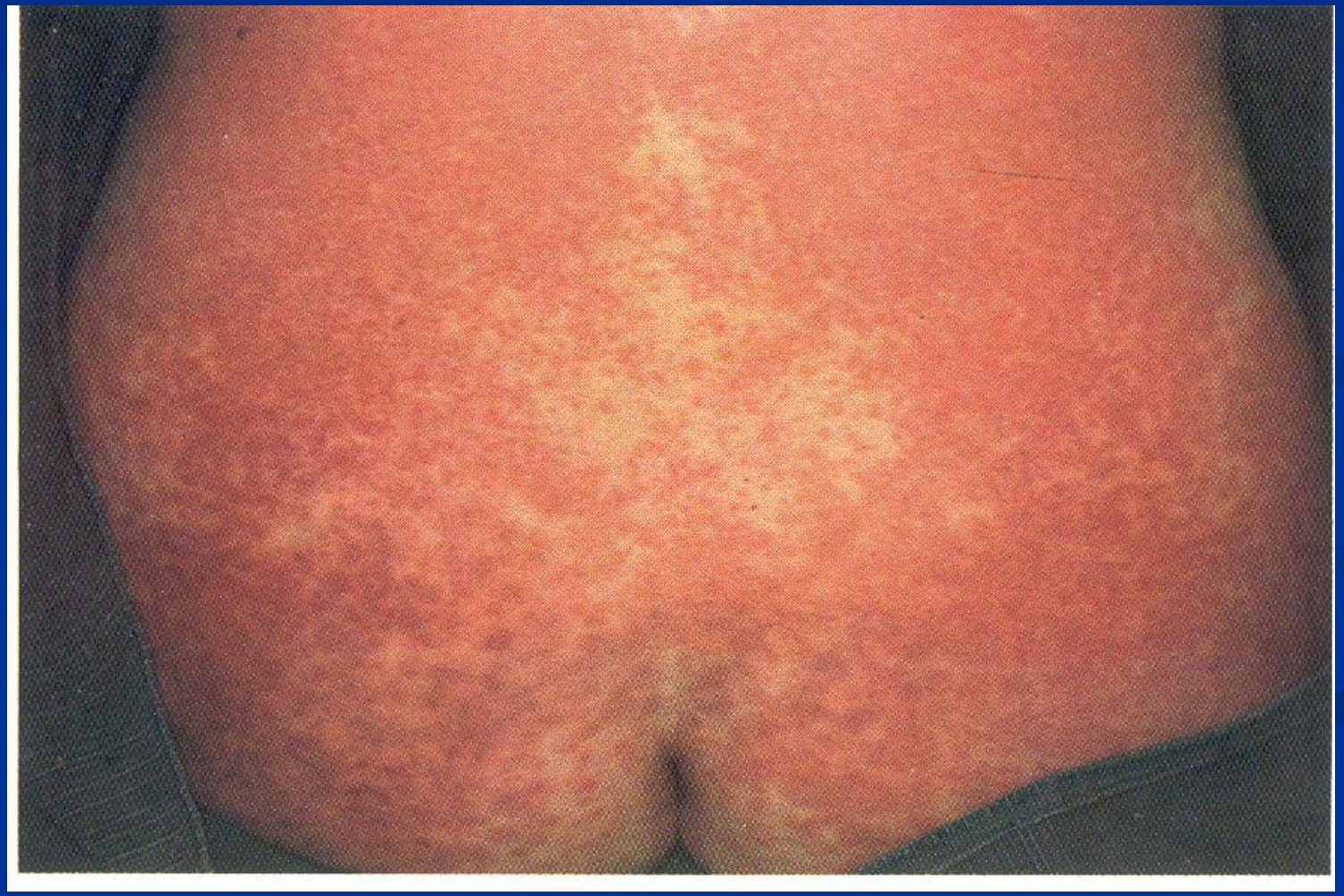


Tonsillitis in mononucleosis

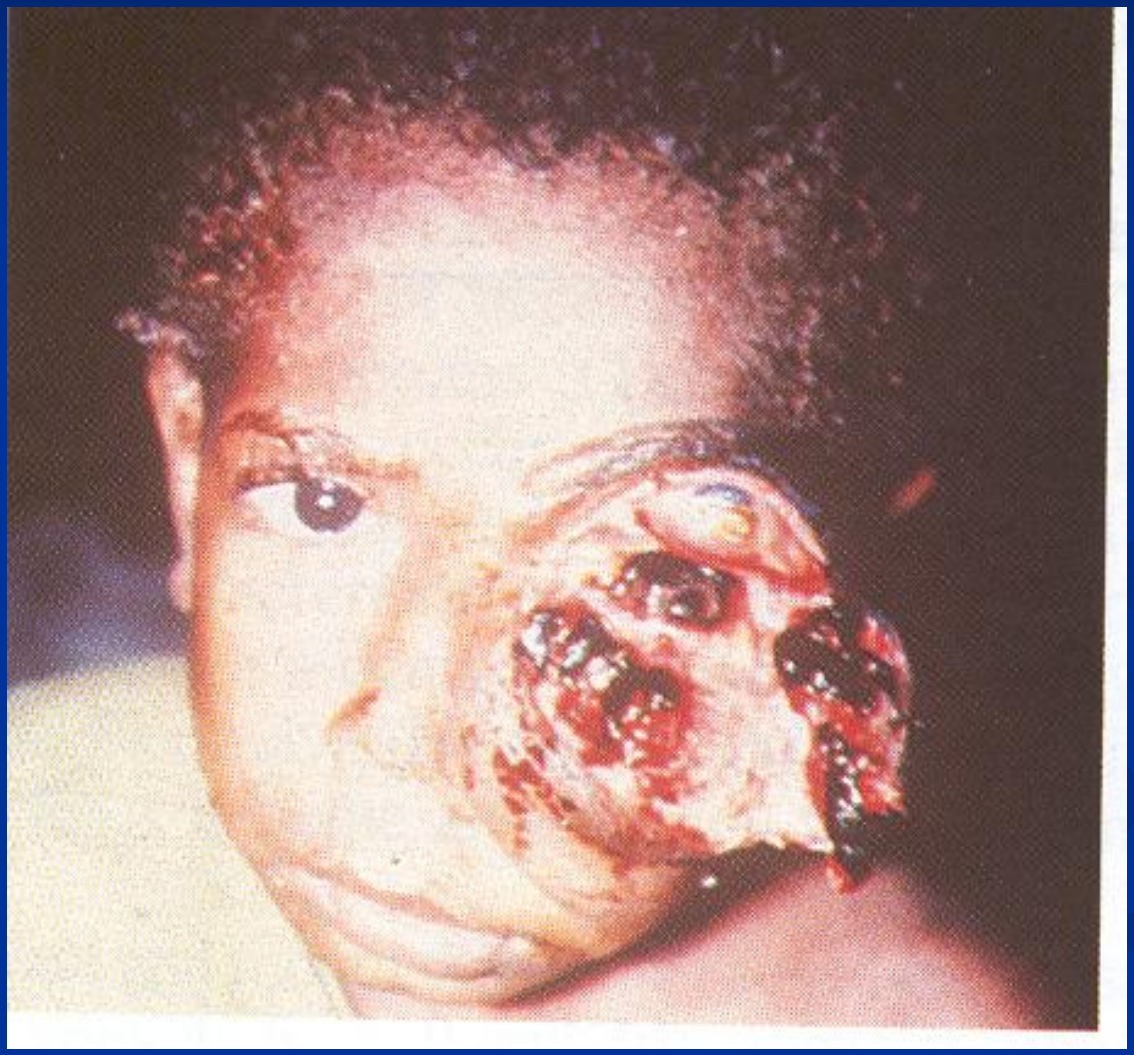




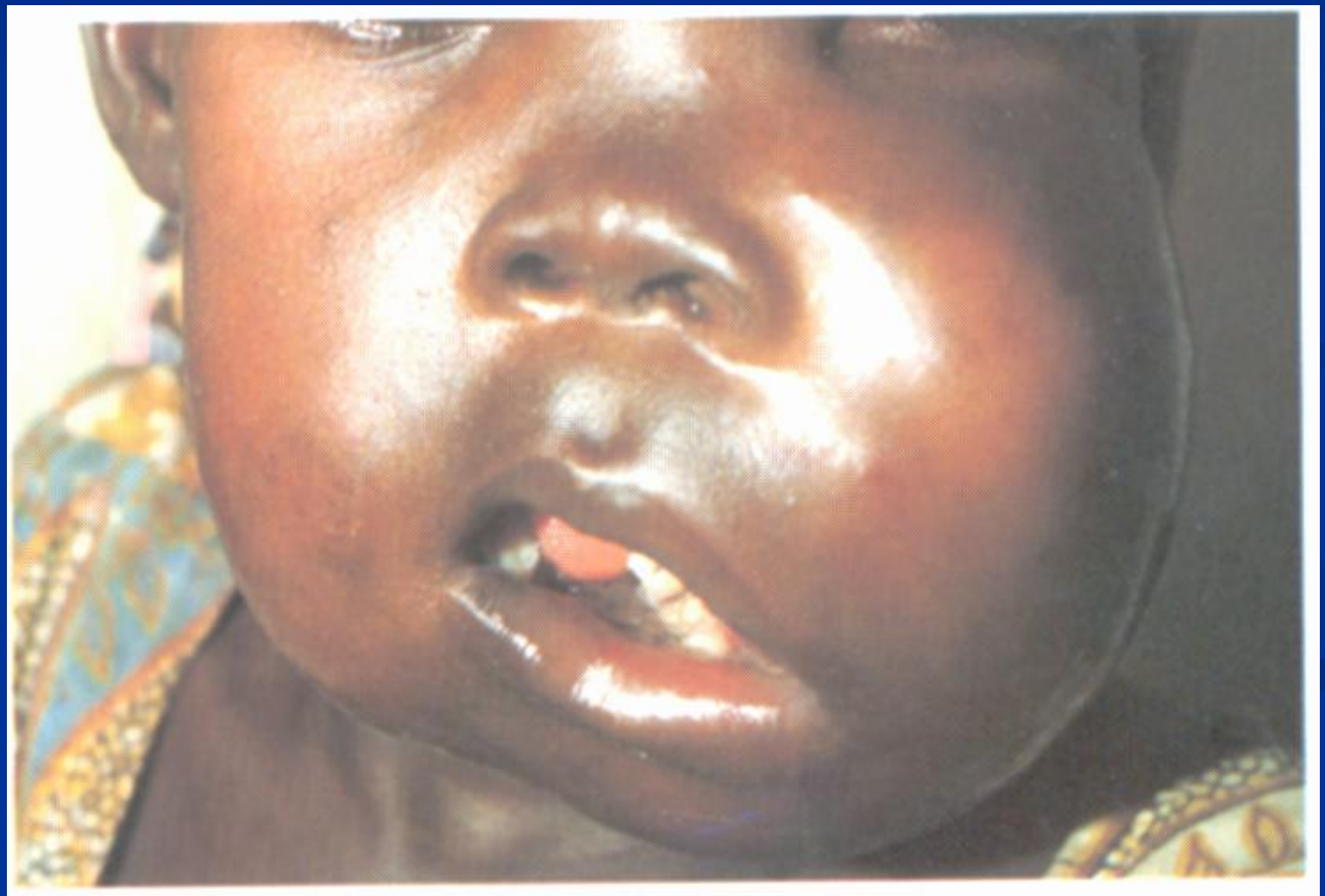
Ampicillin rash in mononucleosis



Burkitt tumor



Burkitt tumor



Diphtheria

Pathogen

- Diphtheria is a serious infection caused by the Gram-positive rod *Corynebacterium diphtheriae*
- Infection spread by airborne droplets, usually from a child with nasal, or laryngeal infection
- *C. diphtheriae* usually attacks the upper airway, especially the pharynx and larynx, but colonization and infection of cutaneous sores may occur.

Epidemiology

- Humans are the only known reserwoir for *C. diphtheriae*
- The primary modes of spread are via airborne respiratory droplets and direct contact with either espiratory secretions or exudate from infected skin lesions
- Fomities can play a role in transmission and contaminated have been caused epidemics
- Current reservoirs for the diseases are obscure
- In endemic conditions 3-5% of healthy individuals may harbor the organism in their throats
- The disease is still epidemic in the developing countries
- As a new epidemic 50412 cases were reported from the previous Sovietunion in 1995, which gradually diminished after the WHO mass immunization program

Pathomechanism

- *C. diphtheriae* produces a potent toxin which causes local tissue necrosis, as well as demage to the heart, peripheral nerves, adrenals and kidneys.
- The toxin produces necrosis of cells and local inflammation by disrupting protein synthesis.
- Tissue necrosis is severe surrounding the area of colonization, and a fibrinous exudate, which containes erythrocytes, bacteria and inflammatory cells, is formed as a pseudomembrane.
- *Often, there is soft tissue oedema in the vicinity of infection which if it occurs in the cervical region is termed „bull neck".*
- The pseudo-membrane can become detached, causing acute obstruction of the airways.

Clinical manifestations 1.

- Symptoms of infection with *C. diphtheriae* occur locally in the respiratory tract, or on the skin
- The incubation period is 2-4 days
- Infection limited to the anterior nares presents with serosanguineous or seropurulent nasal discharge often associated with a subtle whitish mucosal membrane, particularly on the septum
- The discharge can excite an erosive reaction on the external nares and upper lip, but symptoms generally are quite mild, and signs indicating toxin effects are rare

Clinical manifestations 2.

- Faucial, laryngeal, tracheal:
  - The onset is generally abrupt, with low grade fever, malaise, sore throat, mild pharyngeal injection, and the development of a membrane typically on one or both tonsils, with extension variously involve the tonsillar pillars, uvula, soft palate, oropharynx and nasopharynx
  - Pharyngeal infection may spread downward into the larynx, or occasionally the disease may begin there
  - Symptoms then include hoarsness, dyspnoe, repiratory stridor, and brassy cough
  - In the case of further progression serious dyspnoe might develop, the child appears anxious and cyanotic, uses accesory muscles of respiration

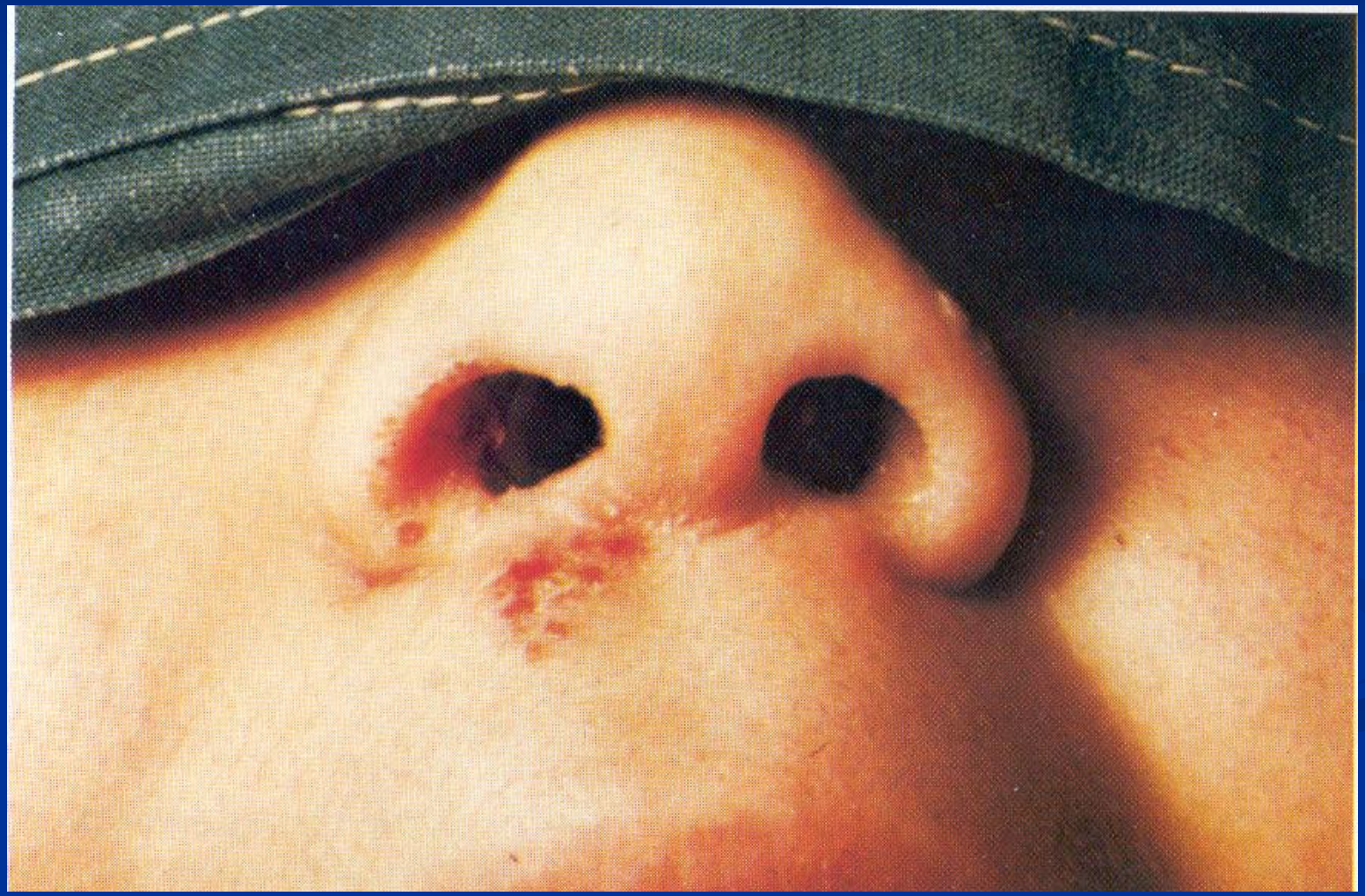
Complications

- Systemic complications are due to diphtheria toxins:
  - Subtle evidence of myocarditis can be detected in as many as two thirds of patients, but 10-25% develop clinical cardiac dysfunction with the risk to an individual patient correlating directly with the extent and severity of the local disease
  - The first evidence of cardiac toxicity occurs after 1 or 2 weeks of illness:
    - Changes of the ECG: ST-T wave changes, 1-st degree AV block
    - Atrioventricular disociation, and other arrhytmias
    - Clinically, myocarditis can present acutelly with congestive failure and circulatory collapse

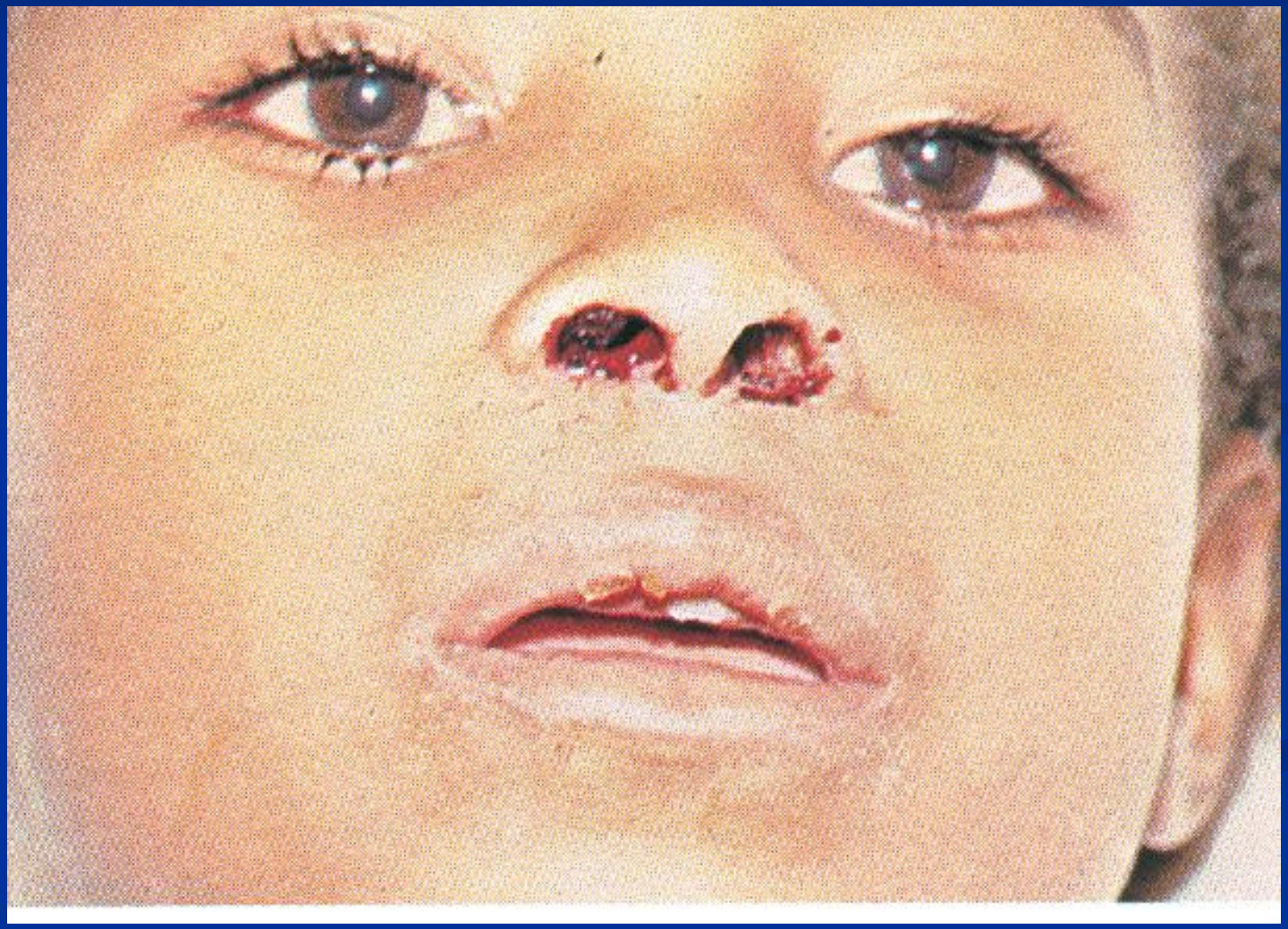
Complications

- Neurological toxicity:
  - This complication is also proportional to the severity of the primary infection
  - Within the first few days of disease, local paralysis of the soft palate and posterior pharyngeal wall occurs commonly, manifested by regurgitation of swallowed fluids through the nose

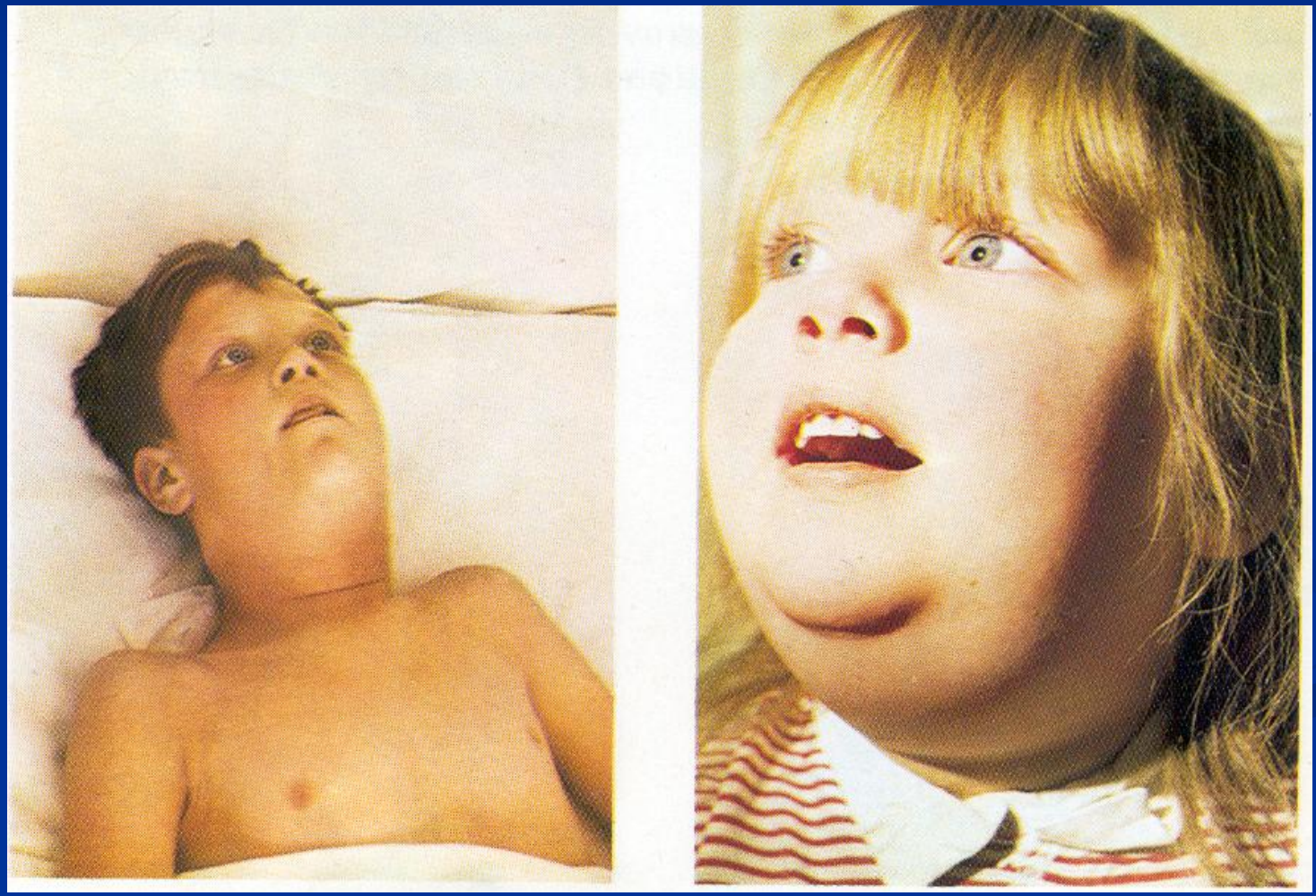
Nasal diphtheria



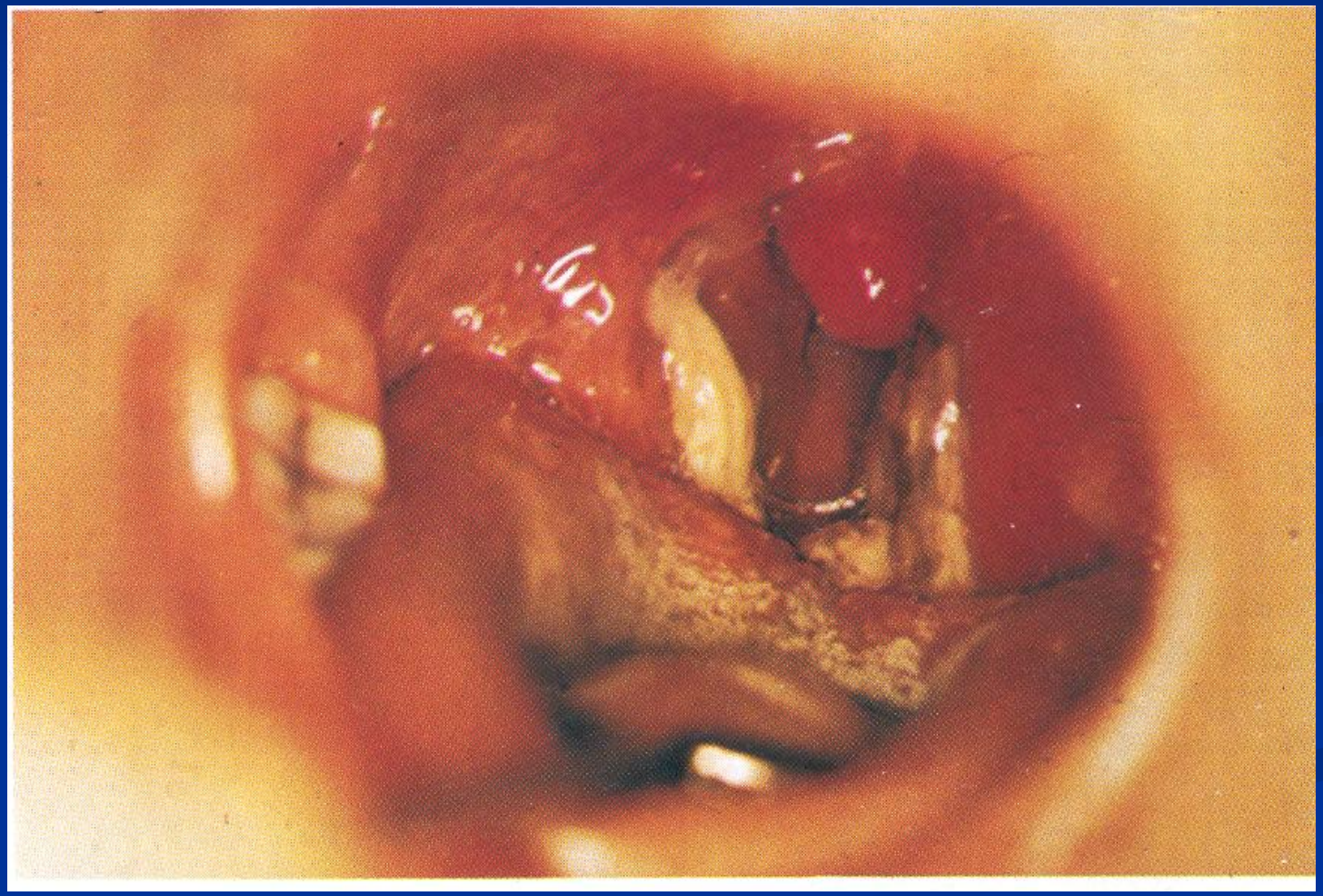
Nasal diphtheria



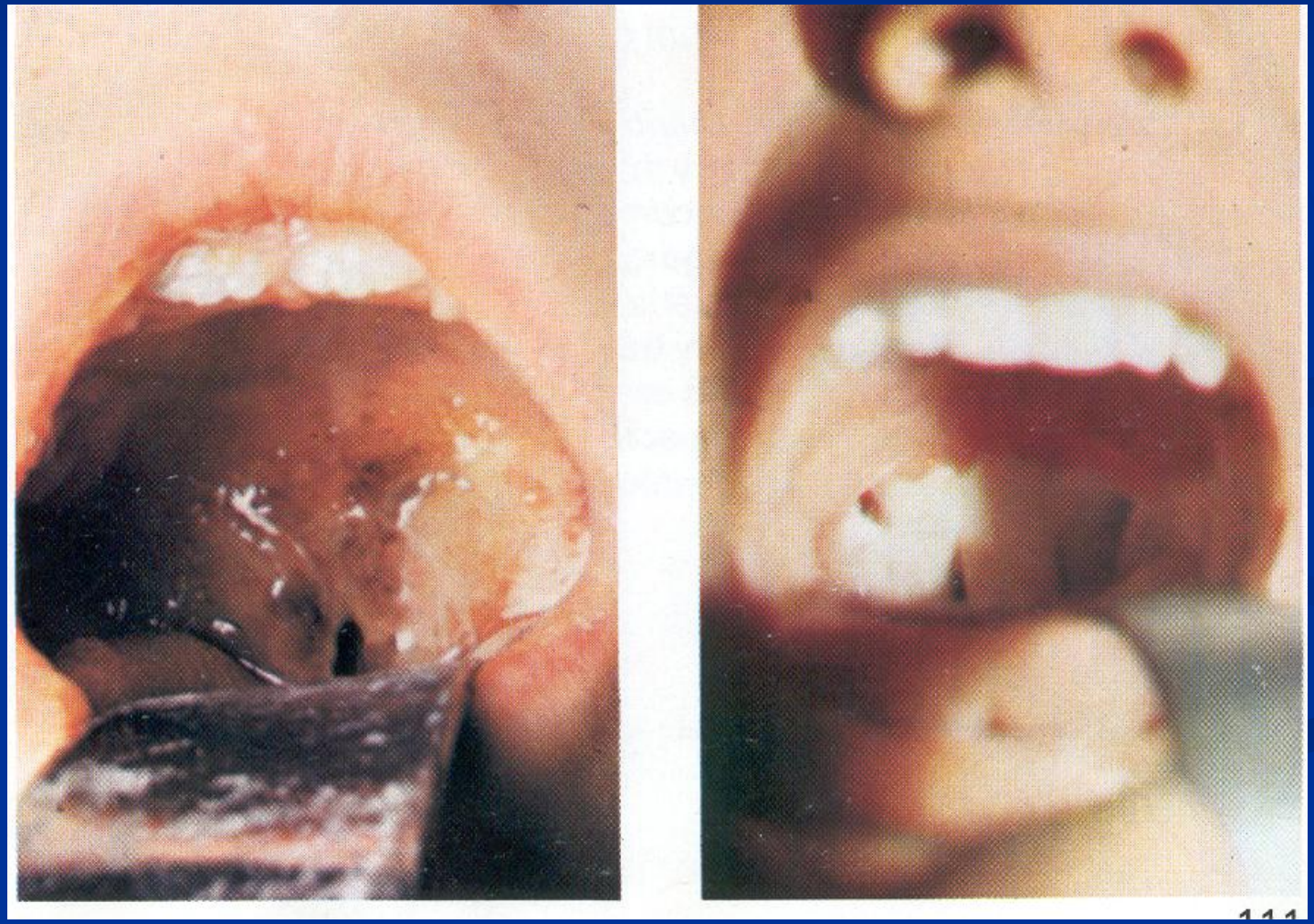
Bull neck in diphtheria



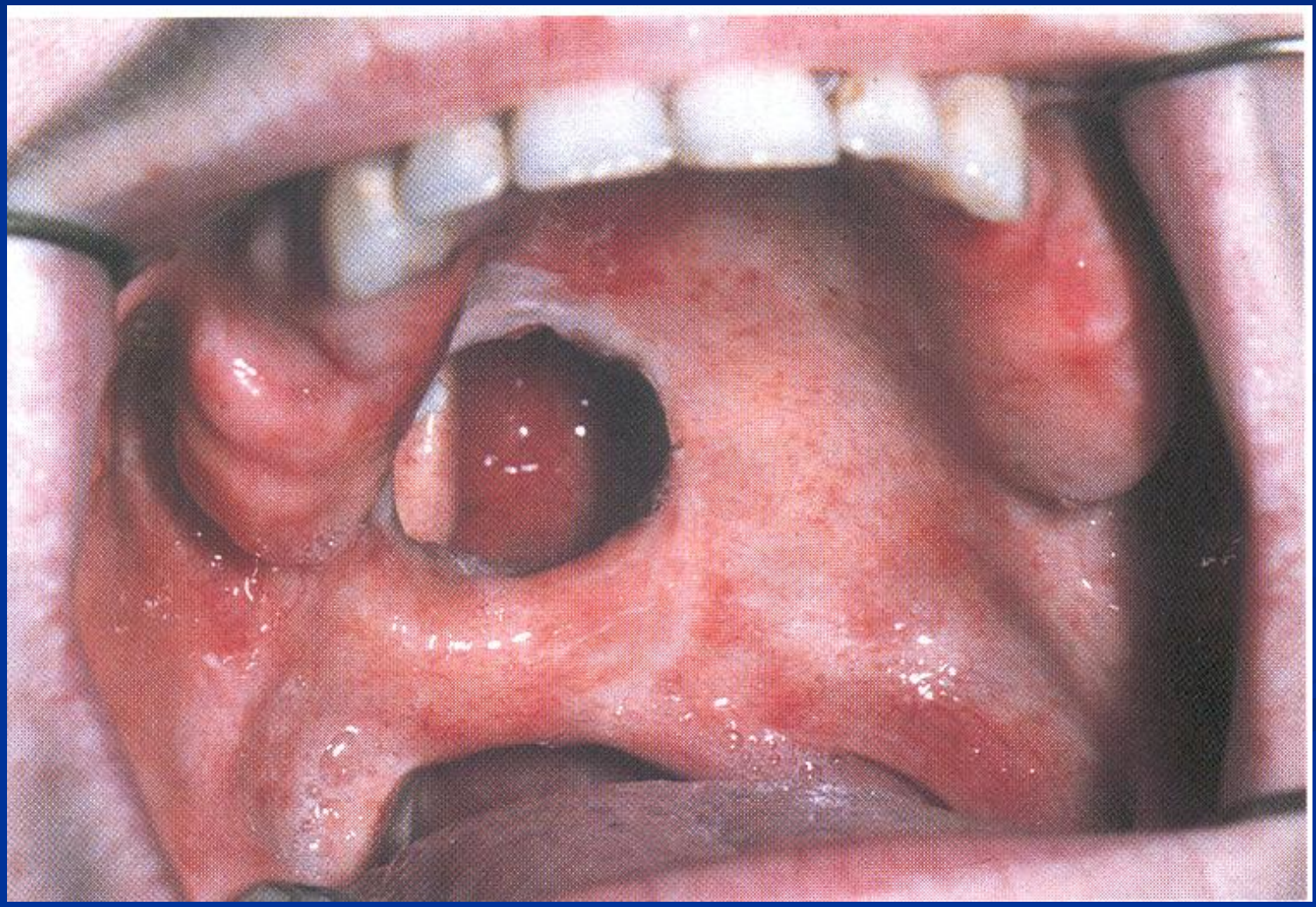
Pharyngeal diphtheria



Pharyngeal diphtheria



Perforation of the soft palate in diphtheria



Serious dyspnoe in diphtheria

Measles

Overview

- Measles is the most frequent cause of vaccine-preventable childhood death, with greatest mortality seen in poor regions of the world where access to basic health-care services is limited.
- Despite the fact that an effective vaccine has been available for more than 30 years, measles has still not been controlled in many parts of the world.
- The disease continues to spread primarily because the degree of vaccine coverage required to interrupt transmission has not been achieved.

Virology

- Measles virus is a spherical, enveloped, single-stranded RNA virus belonging to the genus *Morbillivirus* in the family paramyxoviridae.
- The virion is composed of six structural proteins, three of which form the viral envelope and three the ribonucleoprotein core.
- The nucleoprotein is the major component of the ribonucleoprotein core, the other two parts being the large protein and the phosphoprotein.
- The known measles virus receptors on human cells are the signaling lymphocyte activation molecule (SLAM) CD1506,and the membrane cofactor protein CD46, a regulator of complement activation that plays an important part in protecting host cells from spontaneous complement attack.
- Measles virus has only one serotype and can, therefore, be prevented with a single monovalent vaccine.

Pathophysiology and immunology

- Measles infection is acquired via the respiratory tract, and occasionally through the conjunctivae.
- Virions enter the local lymphatic system, either free or associated with macrophages, and are transported to the regional lymph nodes where they multiply before reaching the reticuloendothelial system.
- The reticuloendothelial infection is followed by a second viraemia through which the skin and the respiratory tract become infected and the disease is manifest after an incubation of 10–12 days.
- The measles rash develops as a consequence of the interaction between T cells and virus-infected cells.

Measles in young infants

- In developing countries, measles is characterised by high incidence and mortality in infants younger than 9 months who are too young to have been vaccinated against the disease, according to the schedule recommended by WHO.
- Infants have a higher risk of mortality and multisystem involvement than older children.
- Young infants are more likely to be secondary cases of measles within a household than index cases, and case fatality when measles is acquired within a household is greater than when it is acquired from outside the house, probably due to the intensity of exposure.

Clinical issues

- In the integrated guidelines for the primary care management of the sick child (IMCI) in developing countries, a child is classed as having measles if he or she has a generalised rash and one of the *following*:
  - cough,
  - running nose, or red eyes
  - children with measles are examined for mouth ulcers, pus draining from the eye,and clouding of the cornea.
- Indications for admission are severe pneumonia, stridor when calm, inability to drink,vomiting, diarrhoea with dehydration, severe malnutrition, convulsions, reduced conscious state, extensive mouth ulcers, or corneal clouding.
- *The early specific sign of measles is the Koplik-spot on the buccal mucosa*

Measles-related pneumonia

- Pneumonia is the most common fatal complication of measles, occurring in 56–86% of measles-related deaths
- Pneumonia arises in 2–27% of a community-based developing country population, and in 16–77% of children admitted to hospital.
- Measles-associated severe pneumonia carries more than twice the risk of mortality that severe pneumonia in children without measles does.

Case management

- *Vitamin A*—Case management of measles is based around giving vitamin A, antibiotics, oxygen, fluids, and good nutrition.
- In 1990, results of a placebo-controlled doubleblinded randomised trial indicated that two doses of 200 000 units of vitamin A reduced the severity and duration of complications as well as mortality of measles in children ill enough to be admitted to hospital.
- Findings of a meta-analysis showed the protective effect of vitamin A on case fatality to be greatest when two doses are given in severe measles in areas with high case fatality.

Case management

- *Antibiotics*—There are at least three approaches to antibiotic use in measles:
  - antibiotics can be given to all children with measles (prophylactic),
  - to all children with indications for hospital admission, or
  - to children with measles-related pneumonia.
- Initial treatment with antibiotics for measles-related pneumonia should be based on the two common causes, *S pneumoniae* and *H influenzae*.
- Persistent fever is an indication to change antibiotics.

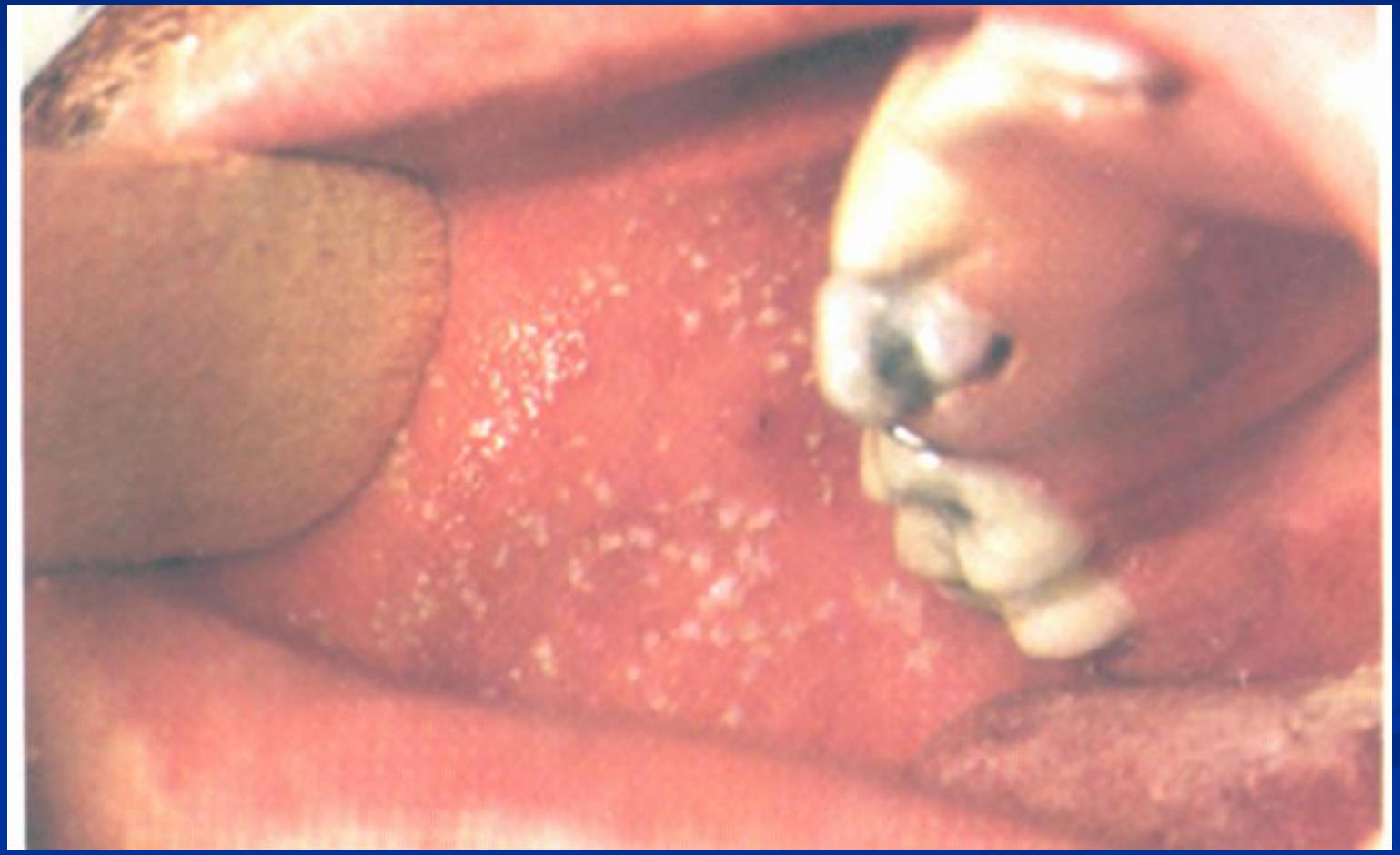
Complications

- Bacterial:
  - Otitis media
  - Sinusitis
  - Pneumonia
- CNS complications:
  - acute postinfectious measles encephalitis (APME),
  - measles inclusion body encephalitis (MIBE), and
  - subacute sclerosing panencephalitis (SSPE).
- The measles infection produces immunosuppression: Immune suppression in measles is multifactorial
- Measles-induced suppression of delayed type (cellular) hypersensitivity responses to tuberculin could persist for a month or two, and can predispose to activation or reactivation of tuberculosis.

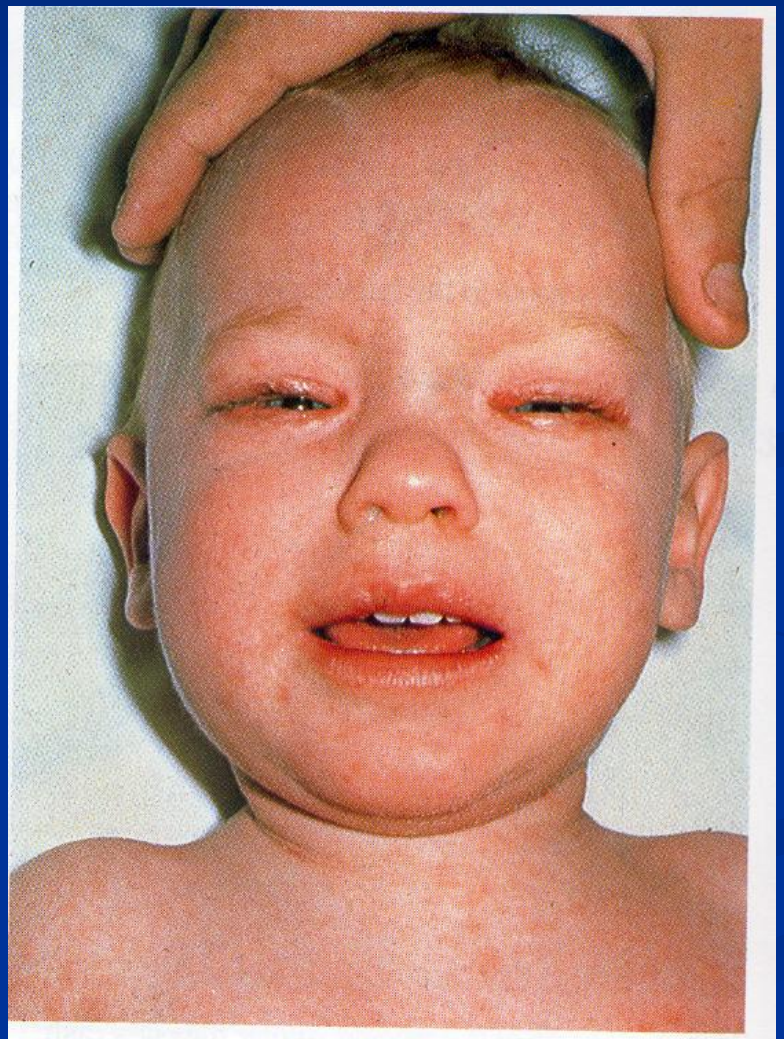
Prevention

- Immunisation of young infants is not recommended,since rates of seroconversion are low. In Bangladesh,infants given standard-dose Edmonston-Zagreb vaccine at age 6 months, for example, had 70% seroconversion, compared with 95% seroconversion when infants were vaccinated at age 9 months.
- This difference is partly explained by the inhibitory effects of maternally derived antibodies, however, other aspects of the young infants immune system could also reduce vaccine response.
- MMR vaccine is used

Koplik spots

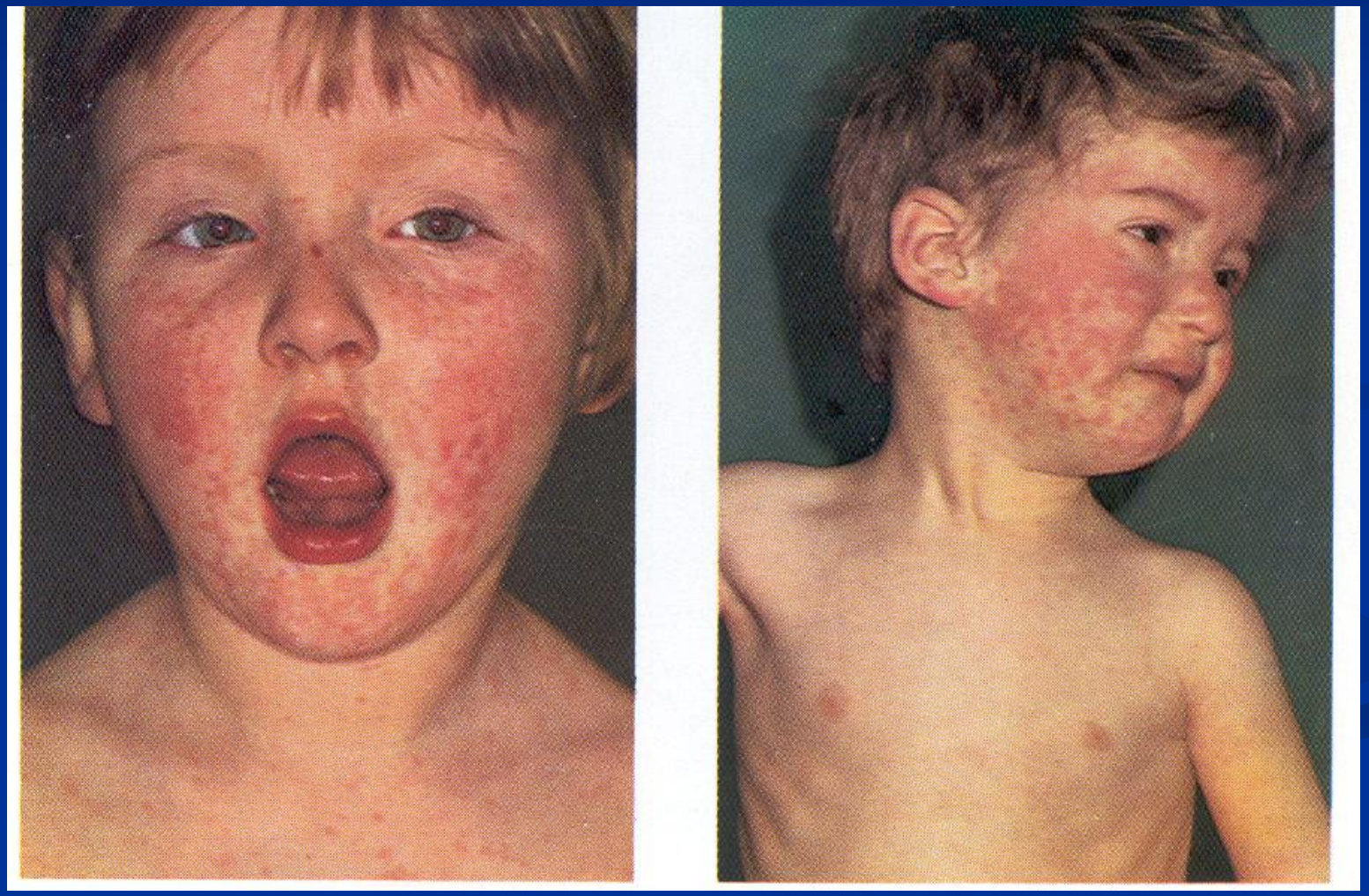


Morbilli face

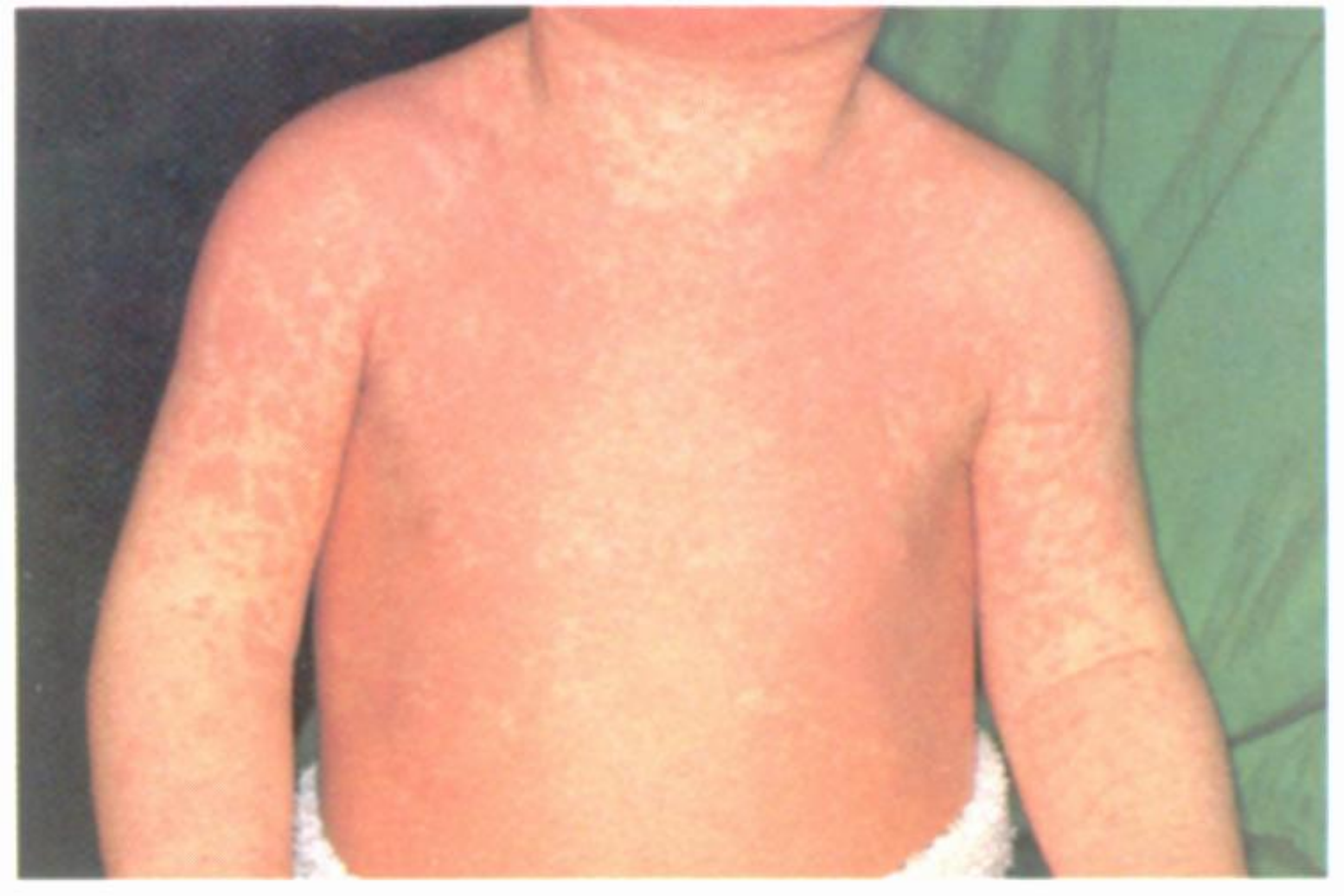


347 A child with measles showing the early clinical

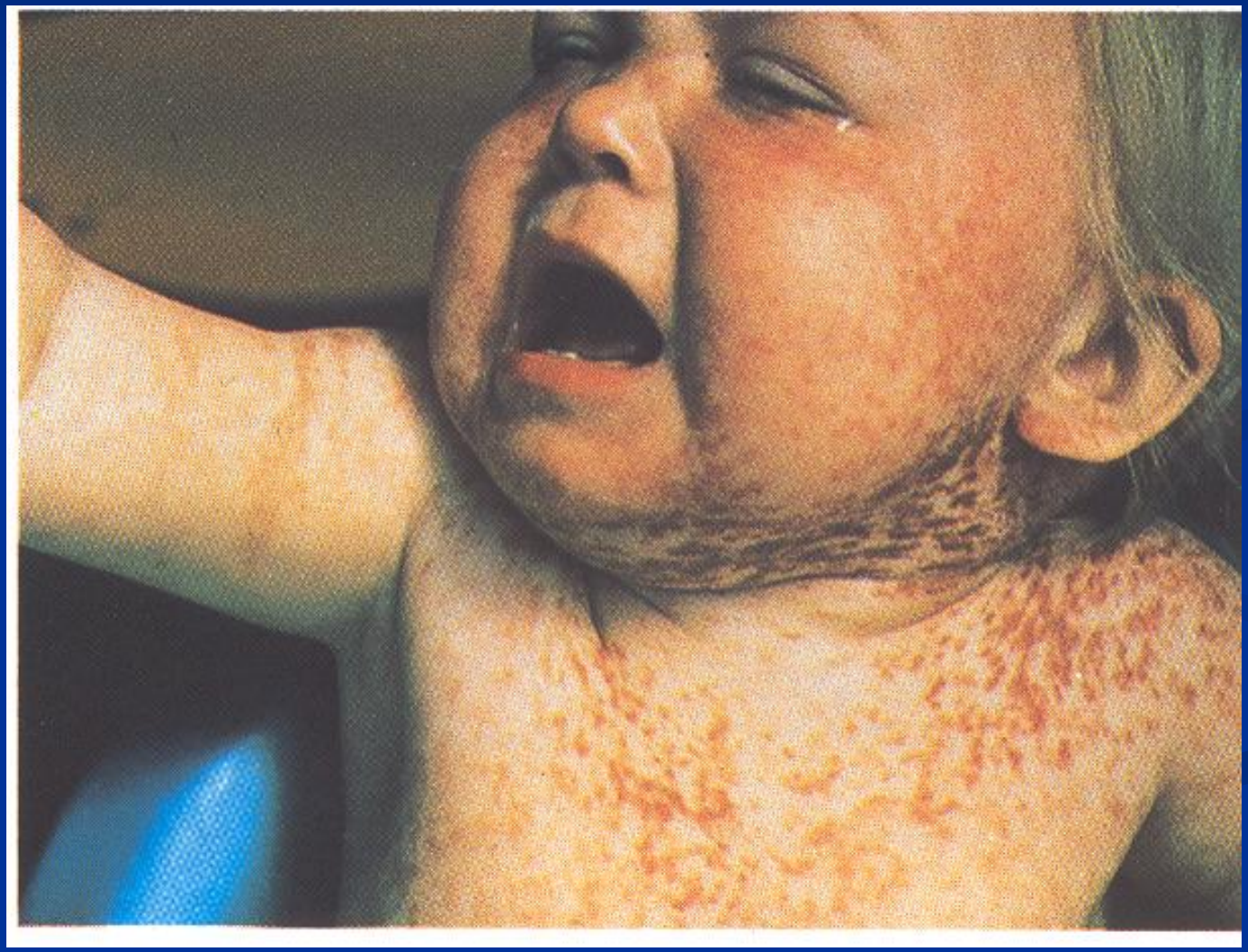
Morbilli rash



Morbilli rash



Haemorrhagic morbilli



Rubella

Introduction

- Rubella was initially known as 'German measles', as it was described first by two German physicians.
- It is generally a mild disease and received little attention until 1941,
- when Norman McAlister Gregg, an Australian ophthalmologist,
- recognised its association with congenital defects.
- The risk of congenital defects was underestimated until the 1960s, when techniques were developed to identify the virus and immune responses to it.
- We now know that there is a >80% risk of congenital defects if rubella is acquired in the first 12 weeks of pregnancy.

The virus

- Rubella virus (RV) is a non-arthropod-borne member of the family Togaviridiae and the sole member of the genus, Rubivirus.
- It is a fragile virus, which is easily destroyed by detergents, heat and extremes of pH.
- RV contains RNA, which is surrounded by a capsid and a lipoprotein envelope.
- The capsid is composed of the capsid protein (C), while the envelope contains two glycoproteins E1 and E2.
- These proteins induce the major immune responses.
- Although there are no major antigenic differences among RV isolates, a number of different genotypes have been identified.
- Identification of genotypes is used to trace the origin of outbreaks as countries approach elimination.

Epidemiology

- RV is only found in humans; there is no known animal reservoir.
- It is transmitted by aerosol via the respiratory tract.
- Rubella is less infectious than measles and influenza and close contact is usually required for transmission to occur.

Symptoms and complications

- Rubella is generally a mild disease in children, but may be more severe in adults.
- It has an incubation period of about 14 days (range 12 - 23 days), before the characteristic nonconfluent maculopapular rash appears.
- This is initially discrete, it appears first on the face and spreads rapidly to the trunk and limbs and may be fleeting or last for up to 3 days.
- Lymphadenopathy may be present before the rash and persist for 10 -14 days after the rash disappears.
- The suboccipital, postauricular and cervical lymph nodes are most frequently affected.
- Adults are more likely to experience a prodromal phase with malaise and low grade fever.

Symptoms and complications

- Headache, sore throat, cough and conjunctivitis may also occur.
- Depending on the population, 20 - 50% of infections are subclinical.
- A viraemia occurs for about 7 days before onset of rash, while virus excretion may be detected from 7 days before rash until 7 - 12 days after onset of rash, thus the patient is potentially infectious for more than 2 weeks.

Symptoms and complications

- Arthralgia and arthritis are the most common complications.
- These occur in up to 70% of postpubertal females, but are relatively uncommon in prepubertal children and males.
- Joint symptoms usually last for 3 - 4 days, but may occasionally persist for 1 month.
- There is no convincing evidence that rubella is a cause of chronic joint disease.
- Other serious complications are post-infectious encephalopathy (about 1 in 6000 cases)

Risk of transmission to fetus and outcome

- There are few prospective studies that have used sensitive laboratory techniques to determine the rate of fetal infection.
- Infection prior to conception does not present a risk to the fetus, but when primary rubella infection occurs in the first 12 weeks of pregnancy rubella virus will cross the placenta and induce a generalised and persistent fetal infection in about 80% of cases.

Risk of transmission to fetus and outcome

- Congenital defects occurred in about 85% of cases infected during the first 12 weeks of pregnancy, with multiple defects most likely to occur in those infected during the first 8 weeks.
- After 12 weeks the risk to the fetus declines rapidly, with only rare cases of deafness reported at 17e18 weeks' gestation.
- The risk of congenital defects may be less when maternal infection is subclinical.
- Spontaneous abortion may occur in up to 20% of cases when rubella occurs in the first 8 weeks of pregnancy.

Laboratory diagnosis and management in pregnancy

- As a clinical diagnosis is unreliable, it is essential that pregnant women developing or exposed to a rubella-like illness in the first 16 weeks of pregnancy are investigated for rubella IgM and IgG in serum obtained as soon as possible, since a termination of pregnancy (TOP) will be offered when rubella is confirmed.11
- Women with a history of rubella vaccination should also be tested, since vaccination fails in occasional vaccinees.
- Tests for parvovirus B19 should also be carried out, as this is associated with hydrops fetalis and fetal death.
- Close collaboration between clinical and laboratory staff is required in order to obtain the necessary specimens and interpret results as rapidly as possible.

Laboratory diagnosis and management in pregnancy

- A pregnant woman with rash:
  - With the serum sample the following information is required: date of last menstrual period, date of onset and distribution of rash and other symptoms such as arthropathy, history of rubella or MMR vaccination and results of any previous rubella antibody tests.
  - A positive rubella IgM result rubella IgG is strongly suggestive of rubella, but should be confirmed by testing a second serum taken 5 - 10 days later to detect rubella IgM and a rise in rubella IgG concentration.
  - Results may be difficult to interpret in women who present more than 4 weeks after onset of symptoms and additional tests available in reference laboratories may be of value.

Laboratory diagnosis and management in pregnancy

- A pregnant woman exposed to a rubella-like illness in the first 16 weeks of pregnancy:
  - Susceptible women are more likely to acquire infection if contact is close and prolonged, such as at home or at work.
  - Women who have only a brief exposure can usually be reassured, although testing is still advised.
  - The serum sample, obtained from the pregnant woman as soon after contact as possible, should be tested for rubella IgG and IgM and if an earlier serum sample is available (e.g. taken for rubella antibody screening), this should be tested in parallel.
  - Although testing of women with a history of rubella/MMR vaccination or a previous positive test for rubella antibodies may seem unnecessary, in practice a woman with a significant exposure should be tested.

Congenital rubella

- Incidence: Congenital rubella has become a rare disease in countries with effective vaccination programmes.
- However, it is important that it is not forgotten, as unvaccinated immigrant women may acquire rubella while visiting their country of origin and give birth to an infant with congenital rubella some months later.
- Cases have also occurred recently in unvaccinated communities in the Netherlands and Canada.

Congenital rubella

- The abnormalities caused by congenital rubella infection are collectively known as congenital rubella syndrome (CRS).
- The classic abnormalities are cataracts, heart defects and sensorineural deafness, but many other abnormalities may be found.
- These can be divided into permanent structural defects, transient abnormalities found in newborns and infants and developmental and late-onset abnormalities.

Transient manifestations

- These include low birth weight, hepatosplenomegaly,meningoencephalitis, thrombocytopaenia +/- purpura and bony radiolucencies.
- These are probably a consequence of extensive virus infection and usually resolve pontaneously within days or weeks.
- Infants with these abnormalities usually have evidence of intrauterine growth retardation and fail to thrive during infancy.

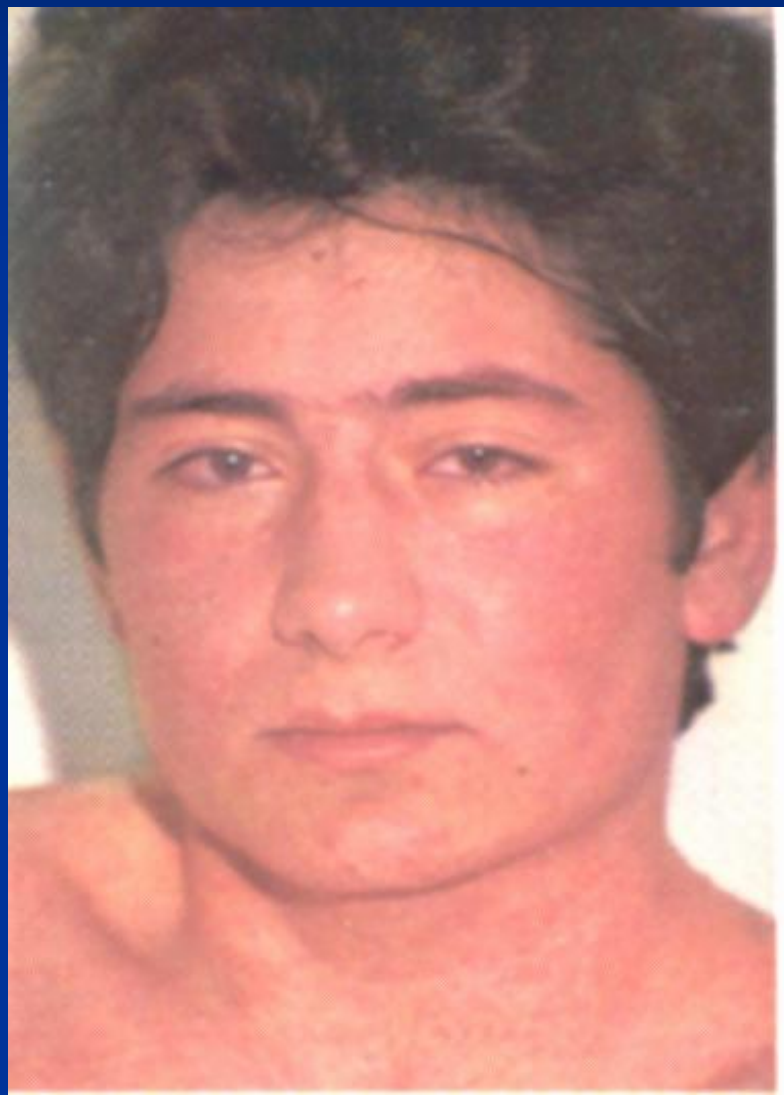
Permanent abnormalities

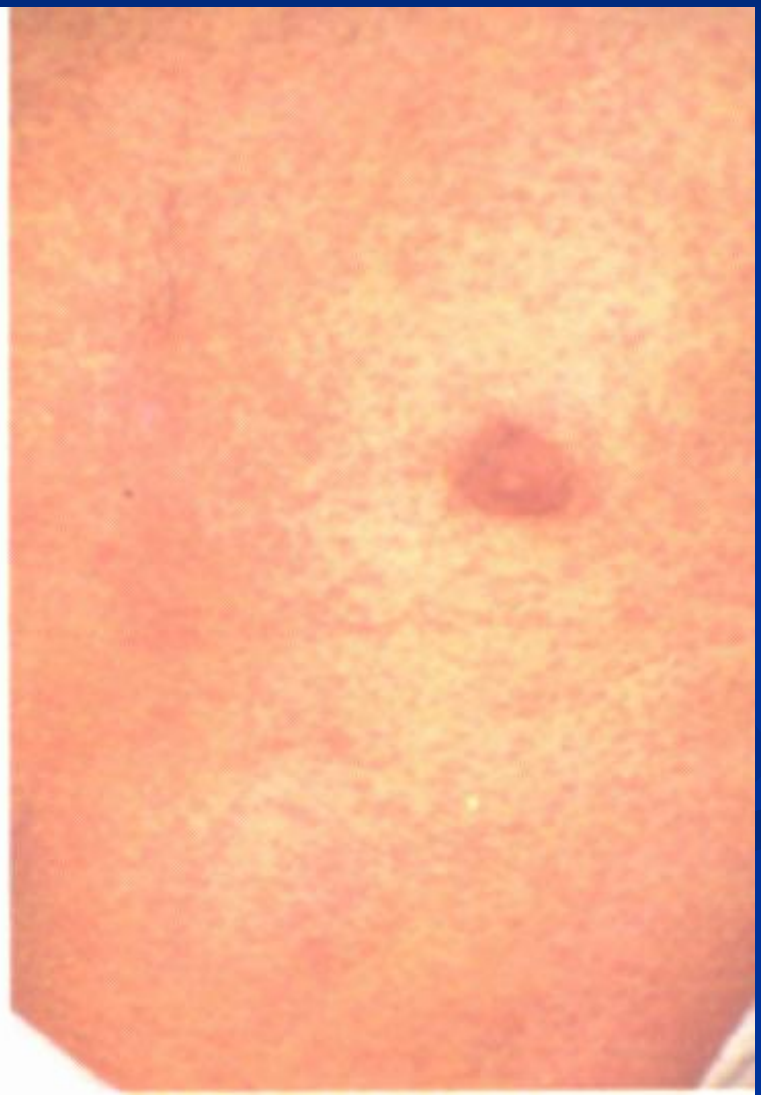
- These include heart defects (e.g. patent ductus arteriosus (PDA), pulmonary artery stenosis, pulmonary arterial hypoplasia), eye defects (e.g. cataracts, iris hypoplasia, microphthalmos, retinopathy), CNS problems (e.g. mental retardation, psychomotor retardation, speech defects/ language delay), microcephaly and sensorineural or central auditory deafness (uni- or bilateral).
- More than half of those children infected during the first 8 weeks of gestation will have heart defects.
- PDA is the most common defect and occurs alone in about 30% of cases.
- Of the eye defects, a 'salt and pepper' retinopathy is the most common.
- Cataracts occur in about one-third of all cases of CRS and in about half of these they will be bilateral.
- Deafness is the most common abnormality and may occur alone, especially when infection has occurred after 12 weeks' gestation.

Developmental and late-onset abnormalities

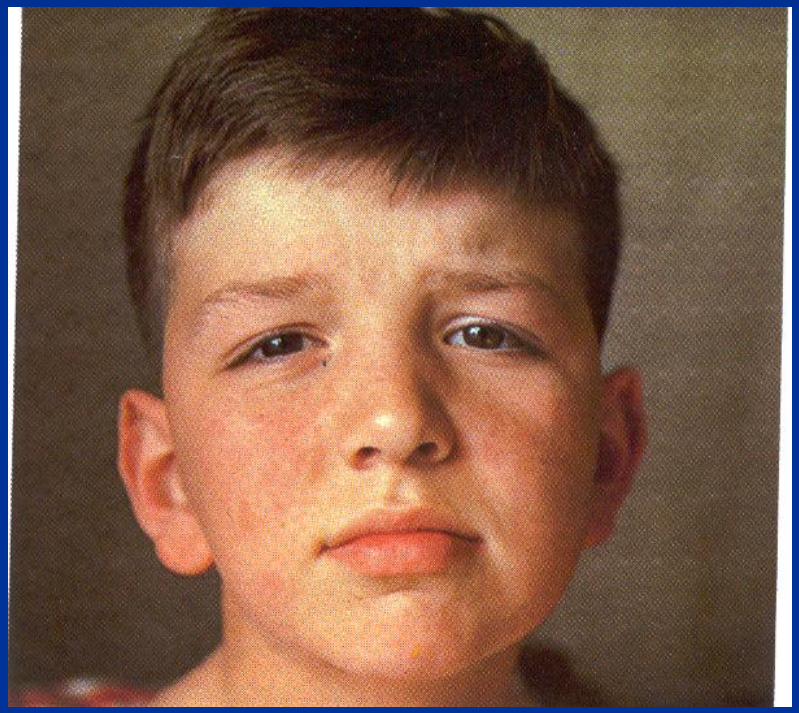
- Congenital rubella is a progressive disease due to persistent virus infection and defects in immune responses.
- Existing manifestations, such as deafness and CNS disease, may progress and some abnormalities may not be detected until the second year of life or later.
- These include hearing, developmental and eye defects, diabetes mellitus, behavioral and educational difficulties and progressive panencephalitis.
- The clinical manifestations and pathogenesis of congenital rubella have been discussed in more detail elsewhere.

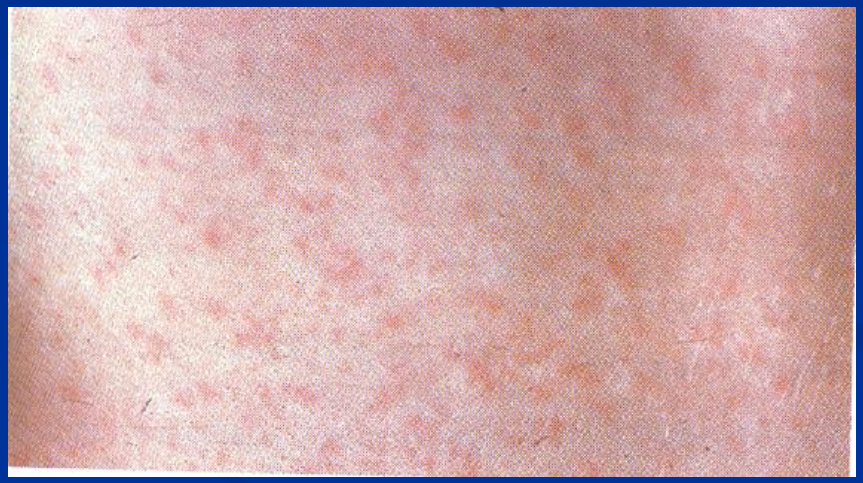
Rubella rash



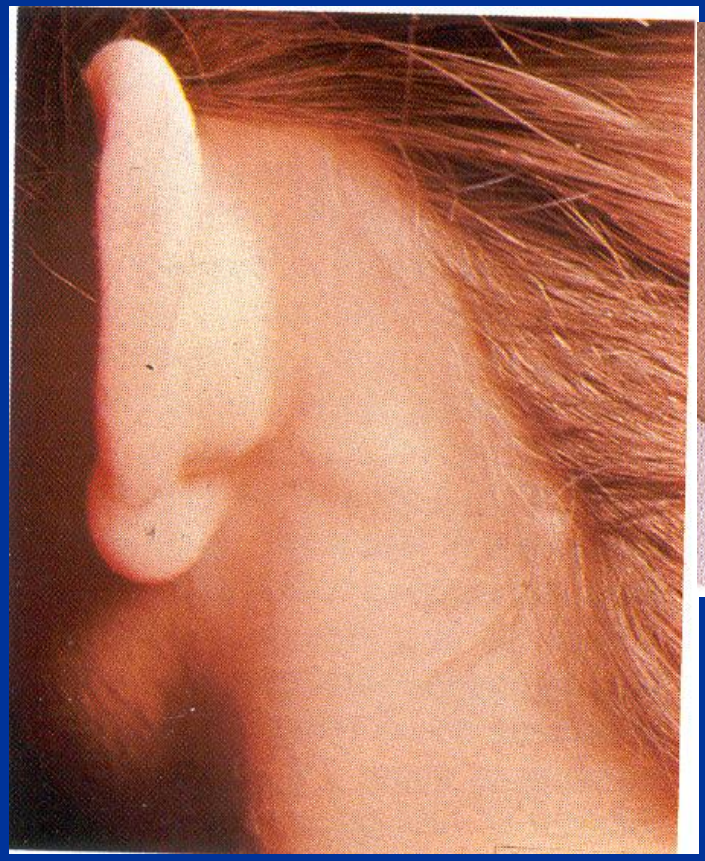


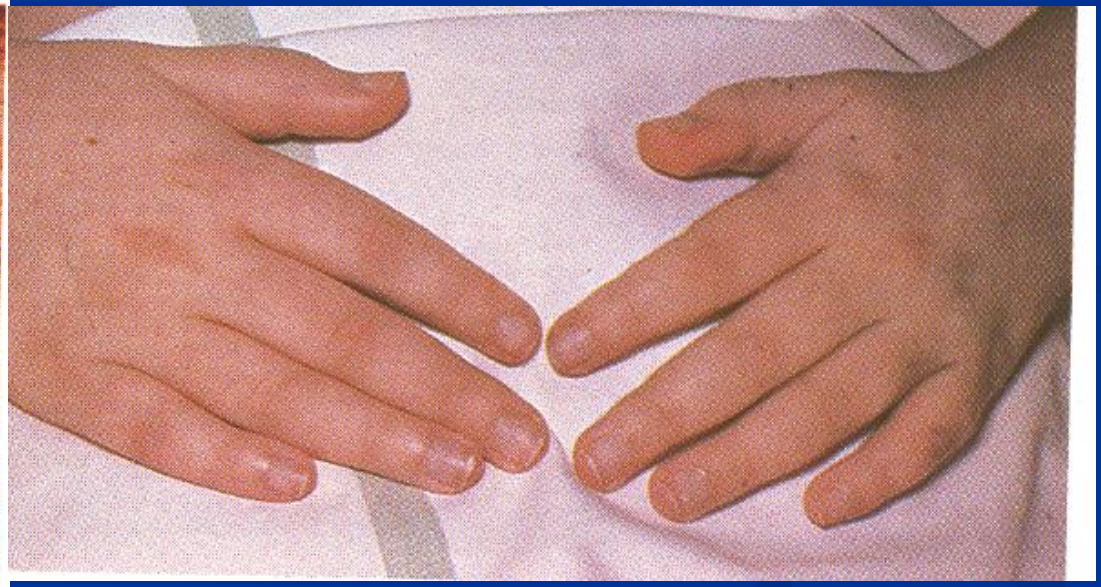
Rubella rush



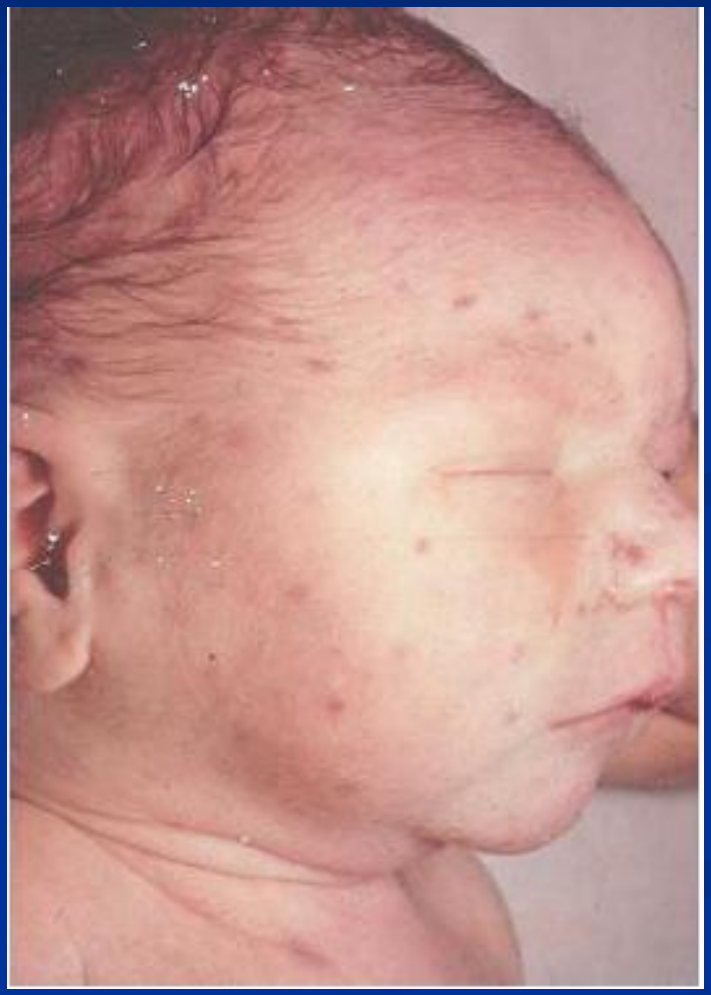


Lymphadenitis and arthritis in rubella

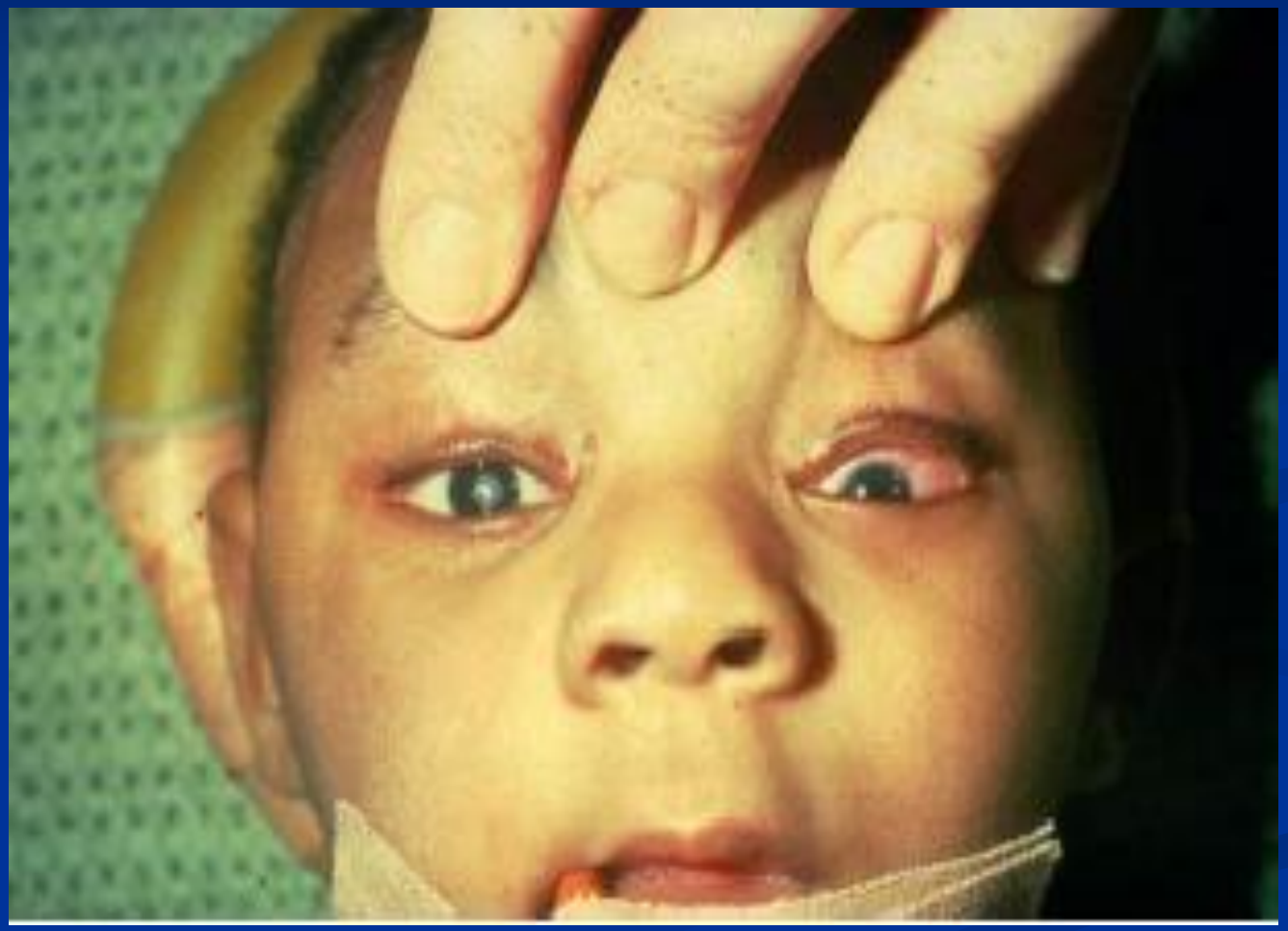




Purpuric rash in a newborn infant



Congenital rubella cataracta in a 9 month old child



Varicella-zoster

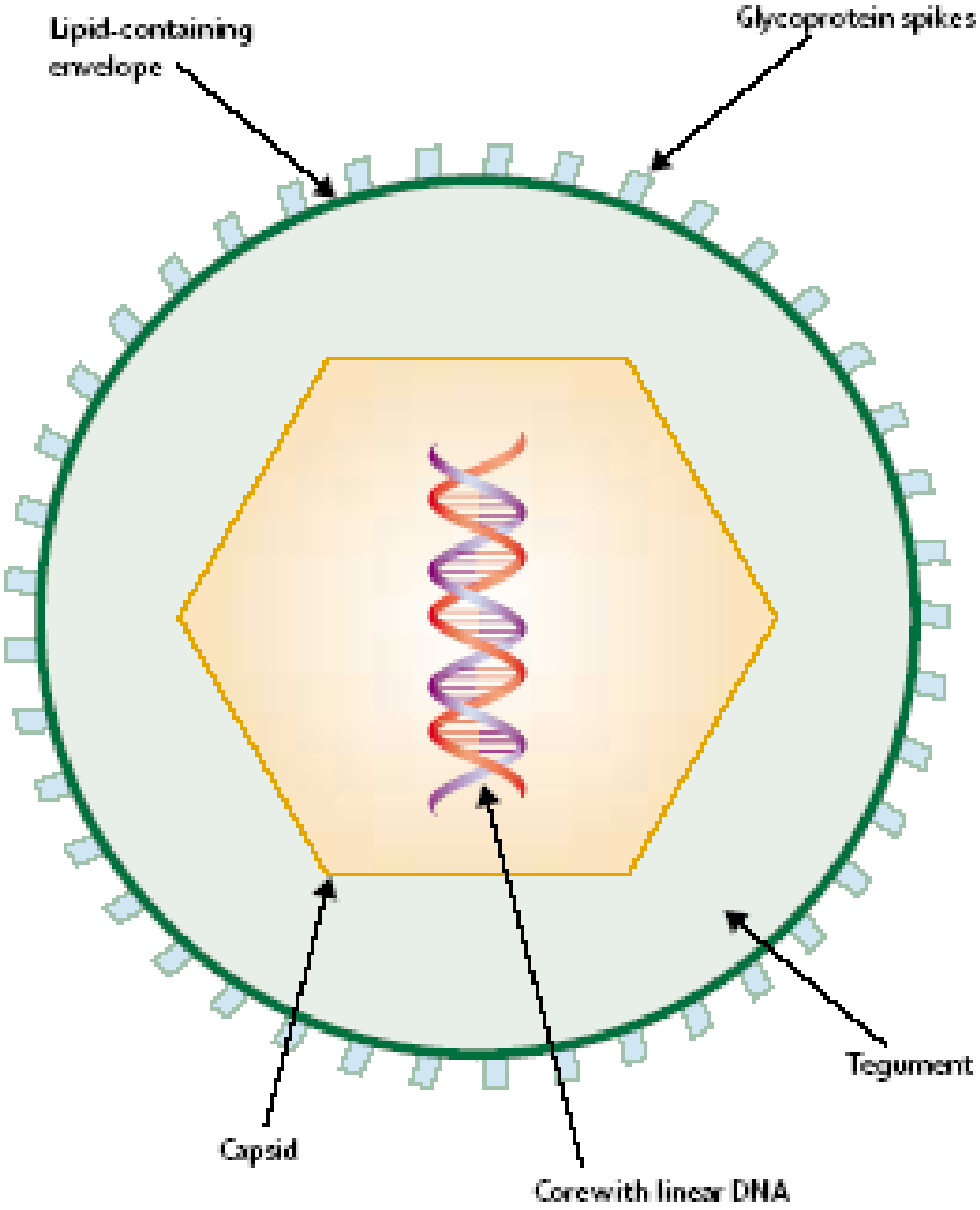
- Varicella-zoster virus is the causal agent of varicella (chickenpox) and herpes zoster (shingles).
- Varicella, the primary varicella-zoster virus infection, is predominantly a childhood disease in non-vaccinated populations.
- It is characterised by a vesicular exanthem, which is frequently accompanied by fever and malaise.
- Although varicella usually results in mild to moderate illness in immunocompetent patients, serious complications (such as central nervous system involvement, pneumonia, secondary bacterial infections, and death) can arise

Varicella cont.

- Varicella is highly infectious, with attack rates in susceptible contacts ranging from 61% to 100%.
- The disease occurs worldwide and is endemic in most populations.
- The disease causes a sizeable societal burden for patients and their caregivers, and can necessitate school absenteeism and work loss.
- After primary infection, the virus persists in sensory nerve ganglia of the dorsal root and establishes latent infection in neuronal cells.
- The virus can reactivate years or decades later and spread unilaterally along a dermatome to cause herpes zoster (shingles), a painful, localised vesicular rash

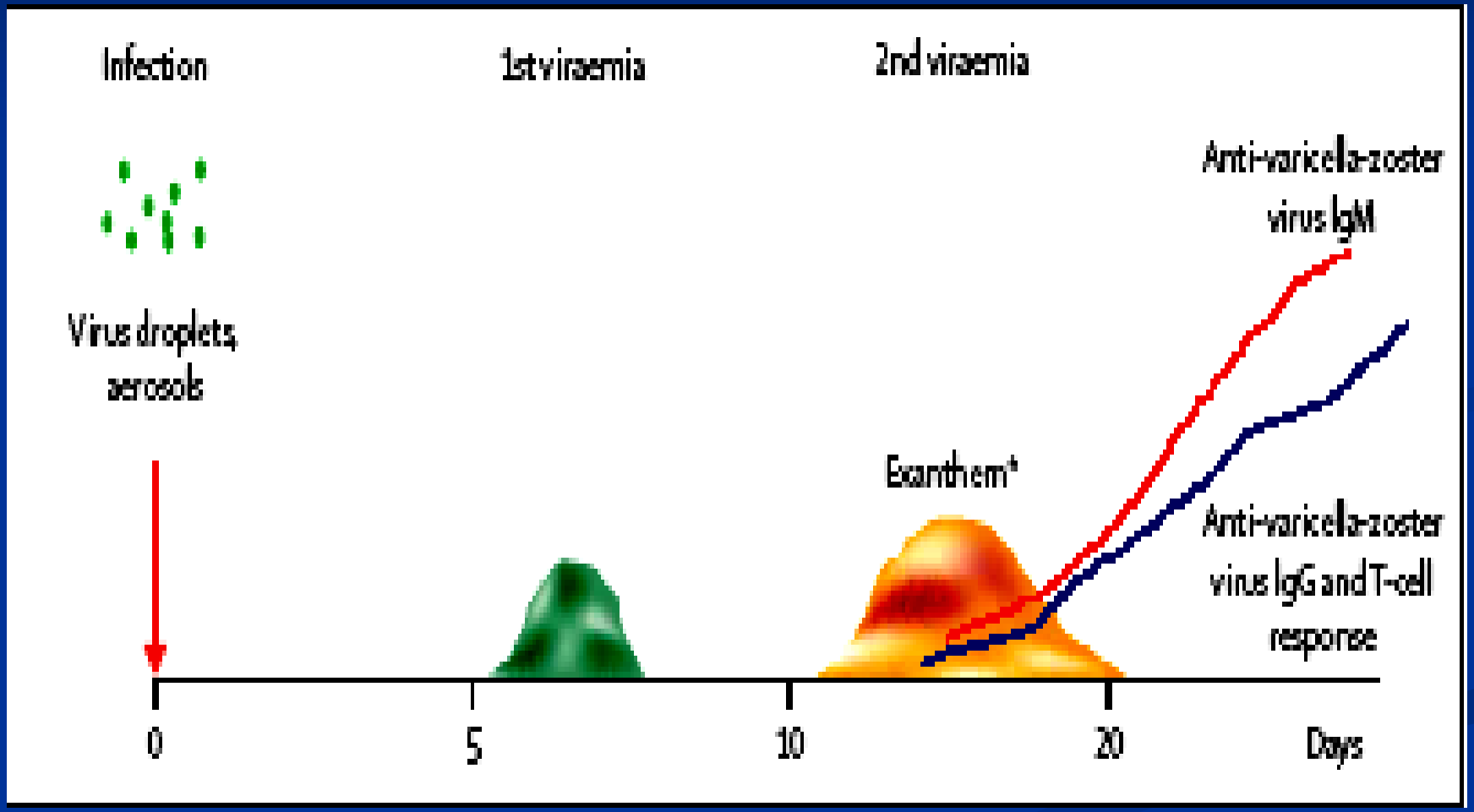
Pathogenesis

- Varicella-zoster virus is one of eight herpesviruses of the *Herpesviridae* family that are known to cause disease in people and some other primates.
- The virus is a DNA α-herpesvirus with a genome of about 125 000 bp that encode 70 genes.
- During primary lytic infection with varicella virus, these genes are expressed sequentially, in much the same way as they are in herpes simplex virus.
- Sequential expression leads to the production of groups of immediate to early non-structural proteins, early nonstructural protein enzymes, and late structural proteins.



The envelope of the virion is composed of glycoproteins that also have important functions in pathogenesis. After infection of a cell, varicella-zoster virus replicates in the nucleus. There, DNA is incorporated into preformed capsids, which leave the nucleus by a first budding event at the inner nuclear membrane. Primary enveloped virions are formed in the perinuclear space. Then the primary envelope fuses with the outer leafl et of the nuclear membrane and the nucleo capsids are released into the cytoplasm. Subsequently virions are re-enveloped at the trans Golgi network, and mature virions are released to the environ ment after fusion of the vesicle membrane with the cell's plasma membrane.

Infection


Infection
1st viraemia
2nd viraemia
Anti-varicella-zoster virus IgM
Virus droplets, aerosols
Exanthem*
Anti-varicella-zoster virus IgG and T-cell response
0
5
10
20
Days

Infection

- The incubation period of varicella is usually 14–15 days (range 10–21 days).
- Varicella-zoster virus spreads by droplets and aerosols from the nasopharynx 1–2 days before onset of a rash, and from skin lesions during the first 5–7 days after appearance of rash.
- This contagious period lasts up to several weeks in immunocompromised hosts.
- The virus is thought to enter a susceptible host via the mucosal surfaces of the respiratory tract, although it is difficult to detect by culture or RT-PCR in this location.

Infection

- Several viral glycoproteins act in concert to adhere to mucosal cells, and allow the virus to enter and spread from cell to cell.
- These glycoproteins also stimulate the host's immune response.
- Varicella zoster virus is thought to multiply in regional lymph nodes before the first subclinical viraemia after about 4–6 days.
- During viraemia the virus disseminates to the viscera, as has been shown in animals and in fetal varicella syndrome.

Infection

- Virus then multiplies further in reticuloendothelial tissues.
- A second viraemic phase occurs about 14 days after infection
- The second viraemic phase promotes viral spread to the nasopharyngeal surfaces and the skin, causing the typical maculopapular–vesicular rash.
- The vesicles contain large amounts of virus, and might be the most important route of viral transmission.
- The period of contagiousness ends when all lesions have crusted

Epidemiology

- The epidemiology of varicella differs in temperate and tropical climates.
- In most temperate climates more than 90% of people are infected before adolescence, whereas in many tropical climates the disease is acquired later in life and adults are more susceptible than are children.
- Epidemiological variation might relate to differences in population density and risk of exposure, differences in transmissibility of the heat-labile varicella/zoster virus in hot, humid conditions, environmental and social factors, or a combination of all these factors.
- Varicella shows pronounced seasonality in temperate climates and most tropical climates, with peak incidence in the cooler, drier months during winter or spring.

Epidemiology

- In temperate climates studies have shown that disease incidence in the total population is in the range of 13–16 cases per 1000 people per year, with substantial year-to-year variation.
- Epidemics tend to arise at intervals of 2–5 years.
- Varicella is a childhood disease, with the highest incidence in children aged 1–9 years.
- Over the last decade, a shift to younger age at infection (below 5 years) has been observed, probably because of
- attendance at child-care centres

Epidemiology

- Older age and a compromised immune system are the most important risk factors associated with severity of varicella disease and death.
- Anecdotal evidence from case reports and case series suggests that varicella in pregnant women is more severe than in non-pregnant women.
- Population-based prospective studies are needed to investigate this possibility.
- In developed countries, average crude varicella mortality rates range from 0·3 to 0·5 per million population, and overall case fatality rates are about 2–4 per 100 000 cases.

Clinical

- Clinical illness is characterised by onset of fever, which is usually concurrent with appearance of the self-limited, pruritic, vesicular rash; various mucosal sites (ie, conjunctivae, oropharynx, and introitus of the genito–urinary tract) can also be aff ected.
- The rash starts as macules, and progresses rapidly through papular and vesicular stages, before beginning to crust within a short period (24–48 h).

Clinical

- The vesicles appear in crops, so that on any one part of the body the rash can be in different stages of development.
- Lesions have a central distribution, and are more concentrated on the face and trunk than on the limbs.
- Varicella lesions are superfi cial and crusts fall off after 1–2 weeks, frequently leaving spots of hypopigmentation that can remain for several months or leave persistent scars.

Clinical

- Varicella commonly causes systemic signs and symptoms including fever, headache, malaise, and loss of appetite or feeding difficulties.
- Secondary cases in household contacts tend to be more severe than primary cases.
- Varicella in previously immunised individuals (known as “breakthrough varicella”) is usually mild, with less than 50 skin vesicles compared with 200–400 lesions in immunologically naive patients; breakthrough varicella also carries a reduced risk of complications.
- Breakthrough varicella can present diagnostic challenges

Clinical

- Complications of varicella illness can be mediated by either viruses or bacteria.
- The most frequent complications are secondary bacterial infections, mainly caused by group A β-haemolytic streptococci or *Staphylococcus aureus*.
- Such infections usually affect the skin and underlying soft tissue.
- Invasive infections (eg, pneumonia, arthritis, osteomyelitis, necrotising fasciitis, and sepsis) can be life threatening.

Clinical

- Complications of the central nervous system range from benign cerebellar ataxia (one in about 4000 cases) to serious manifestations such as meningoencephalitis, meningitis, and vasculitis aff ecting small or large vessels. Intracranial vasculitis causes strokes, most frequently in children.
- Such strokes often happen several months after varicella, and might not be recognised as a complication of the disease.
- Other serious complications include pneumonia and haemorrhages, both can be fatal.

Clinical

- Dehydration and feeding diffi culties caused by varicella disease also frequently require hospital treatment.
- Varicella is especially severe in immunocompromised hosts, for whom there is an increased risk that the virus will disseminate throughout their organs; that new skin lesions will continue to appear for several weeks; that vesicles will become large and haemorrhagic; that varicella pneumonia will develop; and that the patient will have disseminated intravascular coagulation.

Clinical

- Congenital varicella syndrome occurs in 0·4–2·0% of children born to mothers with primary varicella-zoster virus infection during the fi rst 20 weeks of gestation.
- However, cases have been reported as late as the 28th week of gestation.
- This disabling syndrome consists of a character istic sequence of abnormalities, including large areas of scarring on the skin, hypoplastic limbs, chorioretinitis, cataracts and other eye malformations, and brain ab normalities.
- Affected infants are developmentally retarded and their outlook is poor.
- The incidence of varicella during pregnancy varies according to the susceptibility of women of childbearing age and the rate of their exposure to the virus

Diagnosis

- In most cases, the characteristic features of the vesicular varicella rash establish the clinical diagnosis.
- If doubt remains, a recent history of exposure to varicella (or herpes zoster) or the occurrence of secondary cases in close contacts can help diagnosis.
- The differential diagnosis consists mainly of allergic reactions (especially Stevens-Johnson syndrome), generalised herpes zoster or herpes simplex infections, enterovirus infections, pityriasis lichenoides et varioliformis acuta (PLEVA), and guttate psoriasis, and in newborn babies, syphilis and incontinentia pigmenti.
- Before eradication of smallpox and in post-eradication surveillance, varicella was the disease most commonly confused with smallpox.
- Also, congenital histiocytosis can mimic congenital varicella syndrome.

Diagnois

- The most common application of laboratory testing for varicella is to confirm fatal, severe, or atypical illness.
- In countries with varicella vaccination programs, laboratory testing is also needed to distinguish infection with wild-type varicella-zoster virus from vaccine strain infections (by use of restriction enzyme analyses or sequencing of amplified genomic material).
- Additionally, as the disease is controlled or eliminated, such testing is needed to confirm varicella cases, especially in vaccinated people.

Treatment

- In almost all cases, varicella is a self-limited disease, and symptomatic treatment (with acetaminophen to control fever, lotions for pruritus, and fluid substitution to maintain hydration) is sufficient.
- Treatment with acetyl salicylic acid is strongly discouraged in children because of its association with Reye's syndrome.
- Moreover, the use of non-steroidal anti-inflammatory drugs in children with varicella might increase the risk of necrotizing soft tissue infections and invasive group A β-haemolytic streptococci infections: several prospective multicentre case-control studies produced conflicting results, so that this association cannot be ruled out with certainty

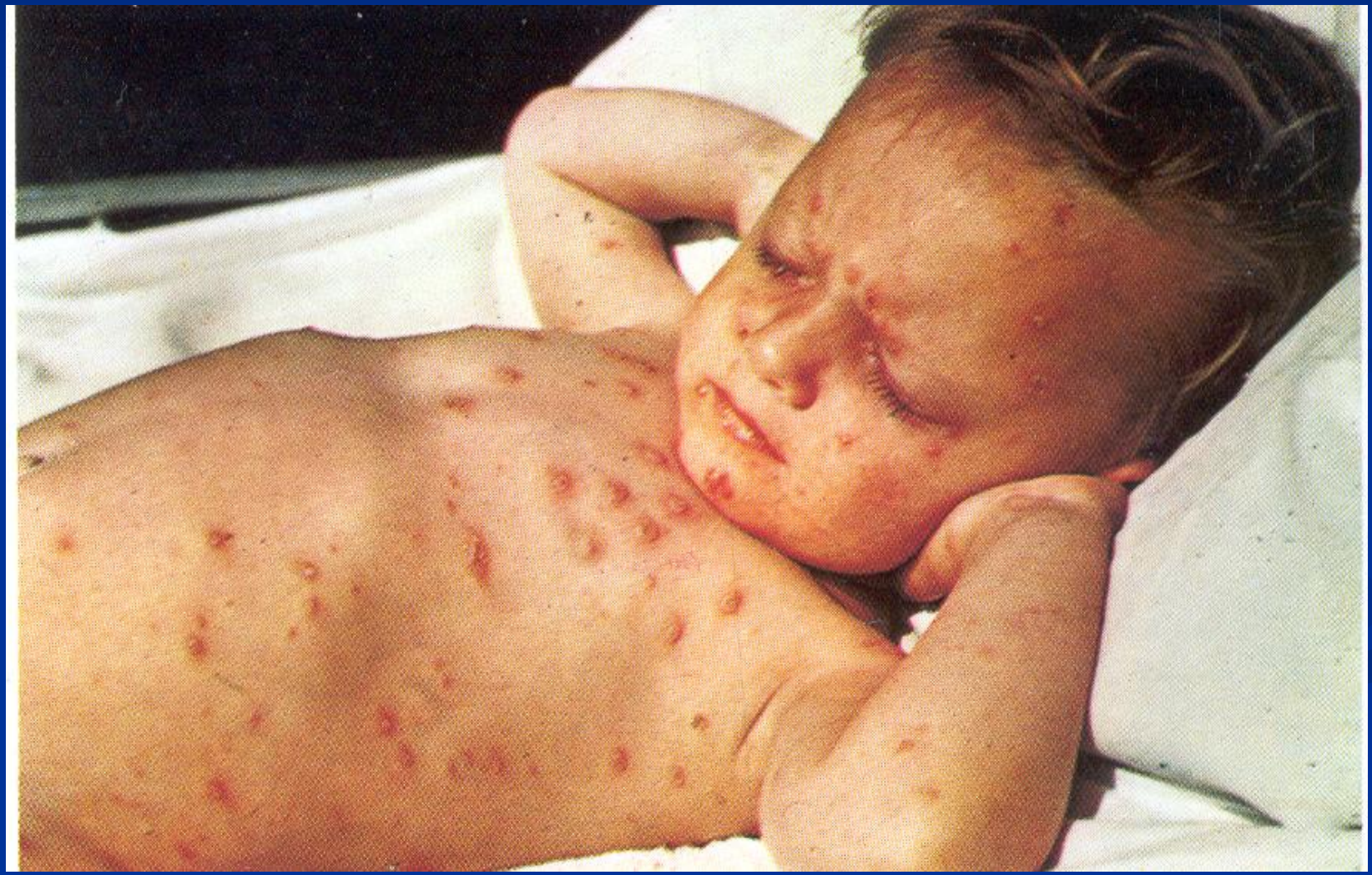
Treatment

- Secondary bacterial infections require rapid administration of antibiotics.
- Treatment with antivirals is mandatory for patients at risk for severe disease (such as immunocompromised hosts and newborns whose mothers acquired infection around the time of delivery) and for any people with varicella-zoster virus infection with virally mediated complications (such as ocular involvement, pneumonia, or encephalitis).
- Acyclovir is most effective if given intravenously within 72 h of onset of disease.
- The recommended daily dosage for children is 1500 mg/m² per day; for adolescents and adults it is 30 mg/kg per day in three divided doses

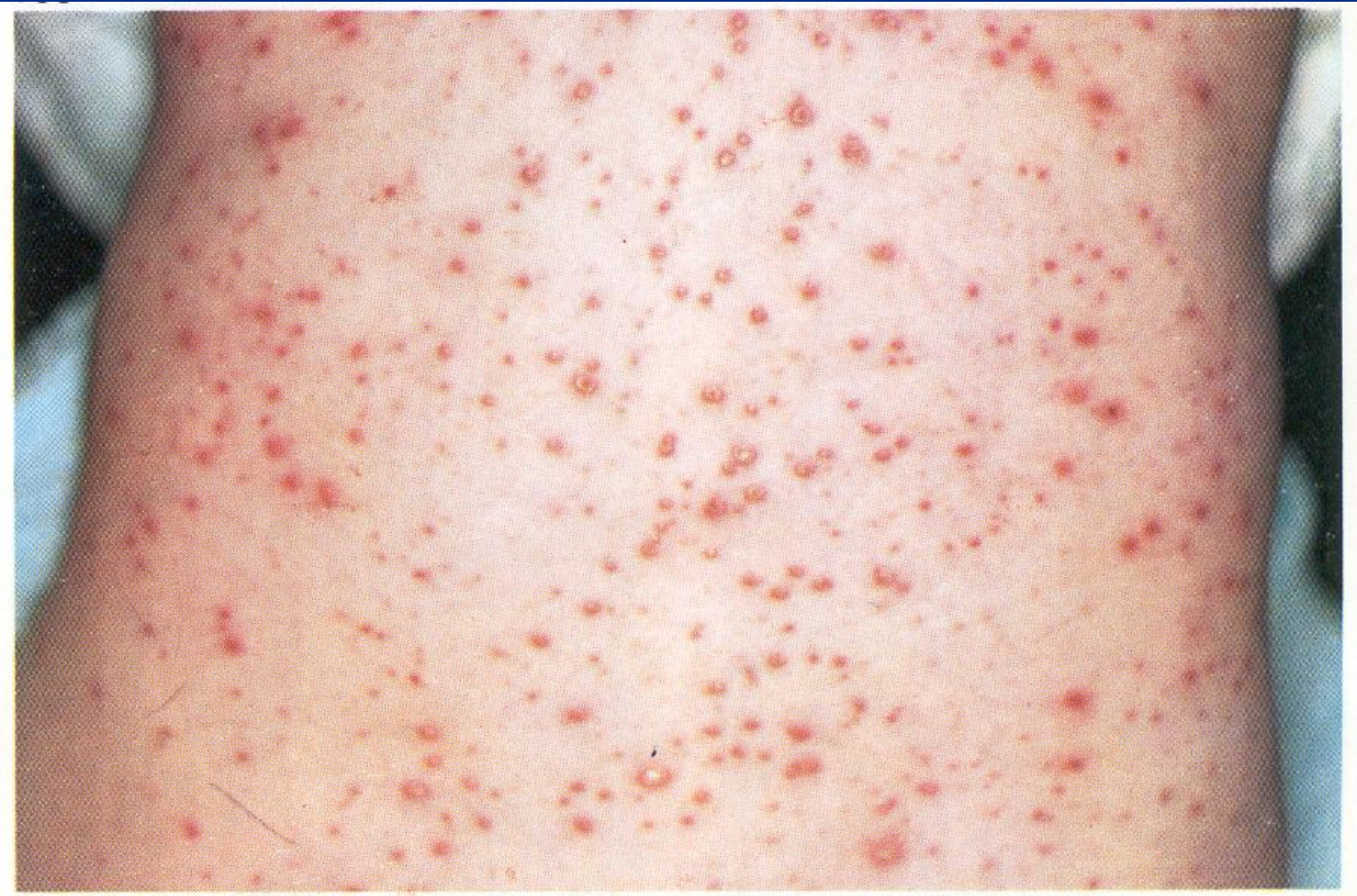
Prevention

- The available varicella vaccines are a single antigen vaccine and a combination vaccine against measles, mumps, rubella, and varicella (MMRV).
- The live, attenuated varicella vaccine is available worldwide as Varivax (Merck, NJ, USA), Varilrix (GlaxoSmithKline, Rixensart, Belgium), and Okavax (Biken, Osaka Japan).
- All vaccines use the Oka strain of varicella-zoster virus, which was isolated from a healthy child with varicella and attenuated by sequential passage in cell culture

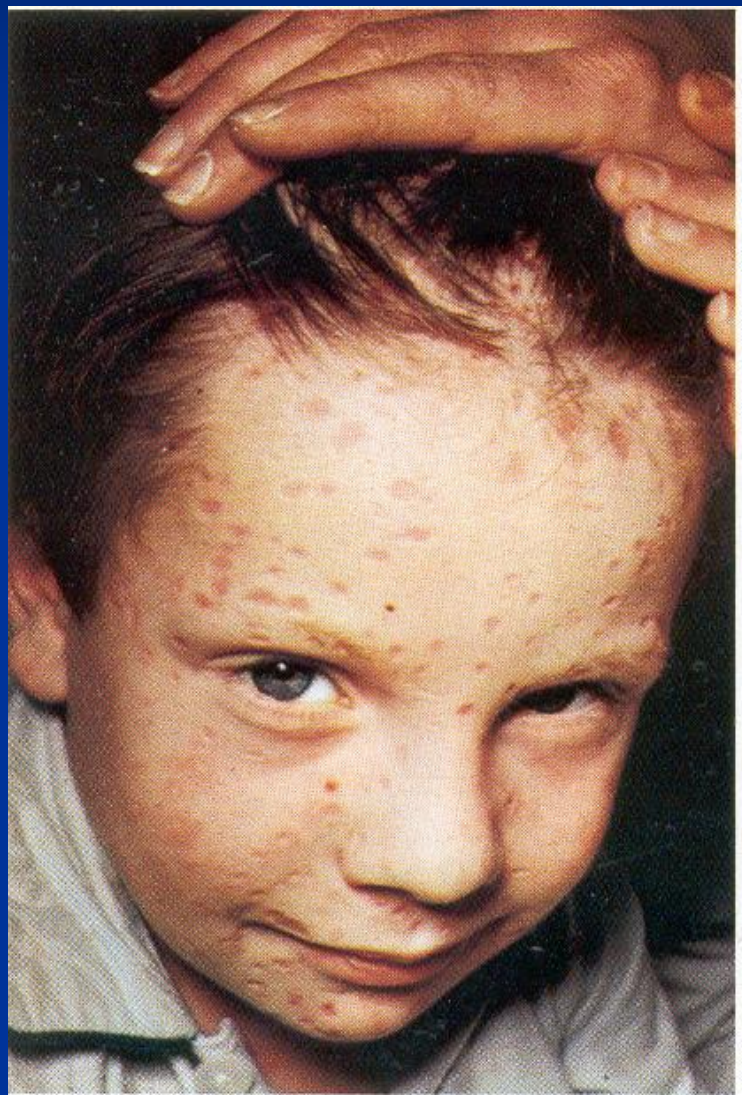
Jellegzetes varicella

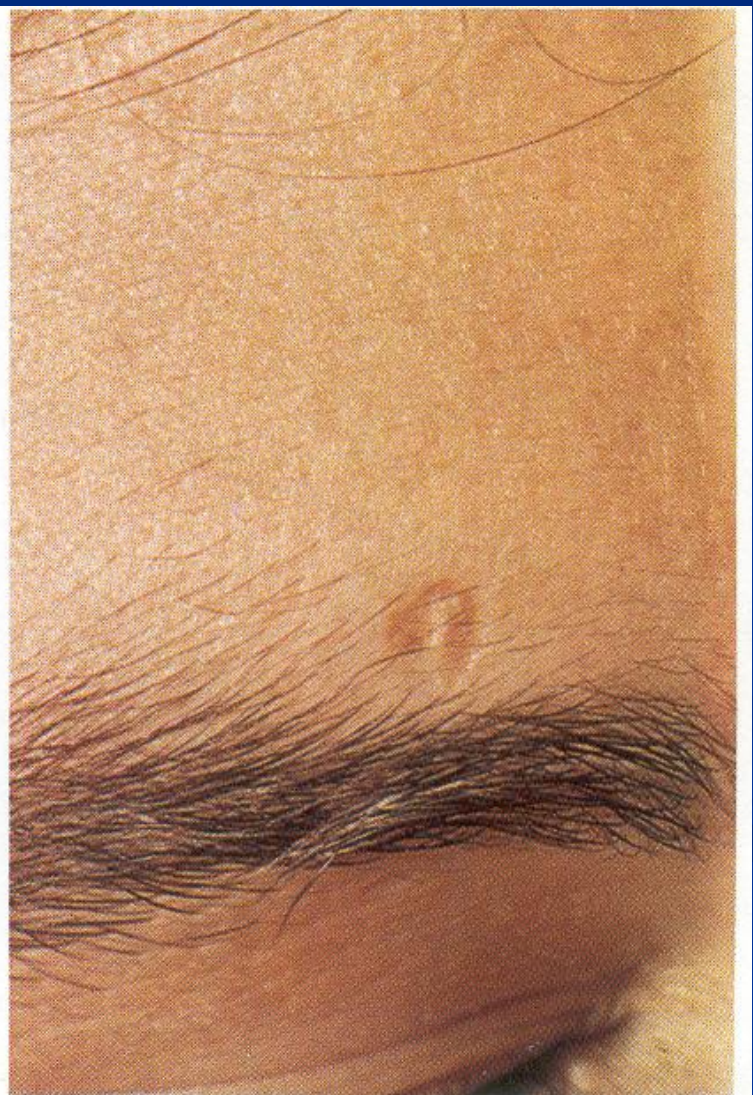


Varicellás bőrelváltozások közelről

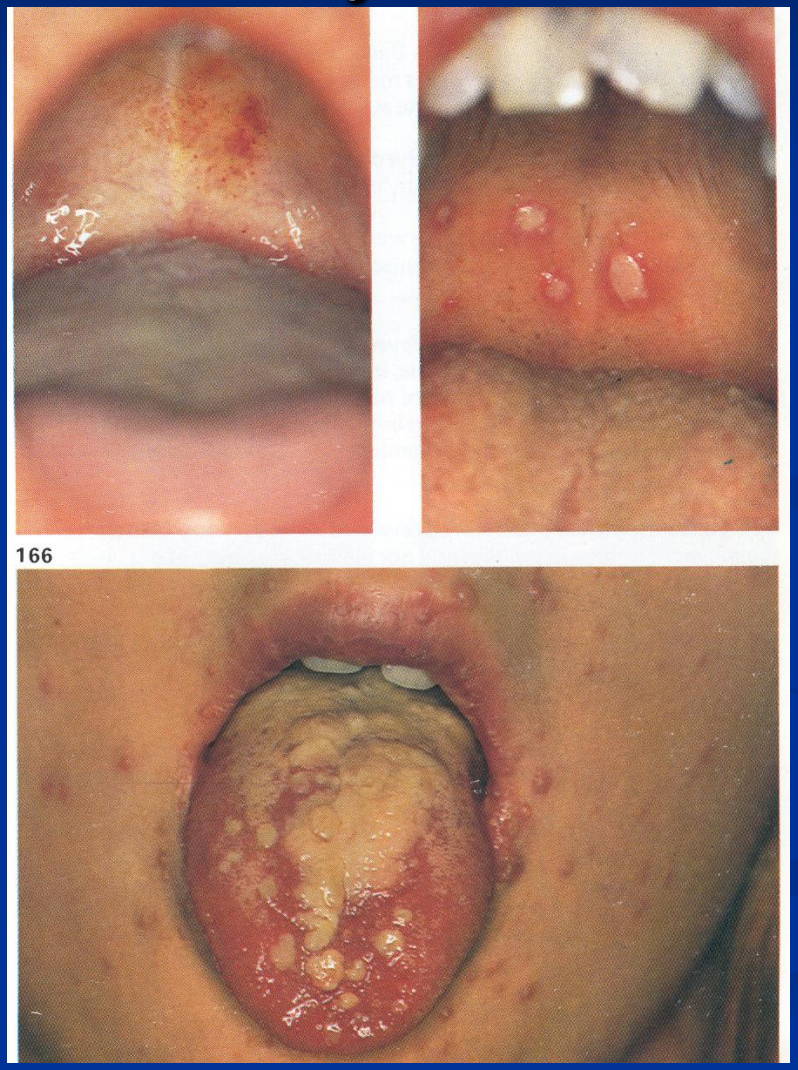


Varicellát követő felületes hegesedés

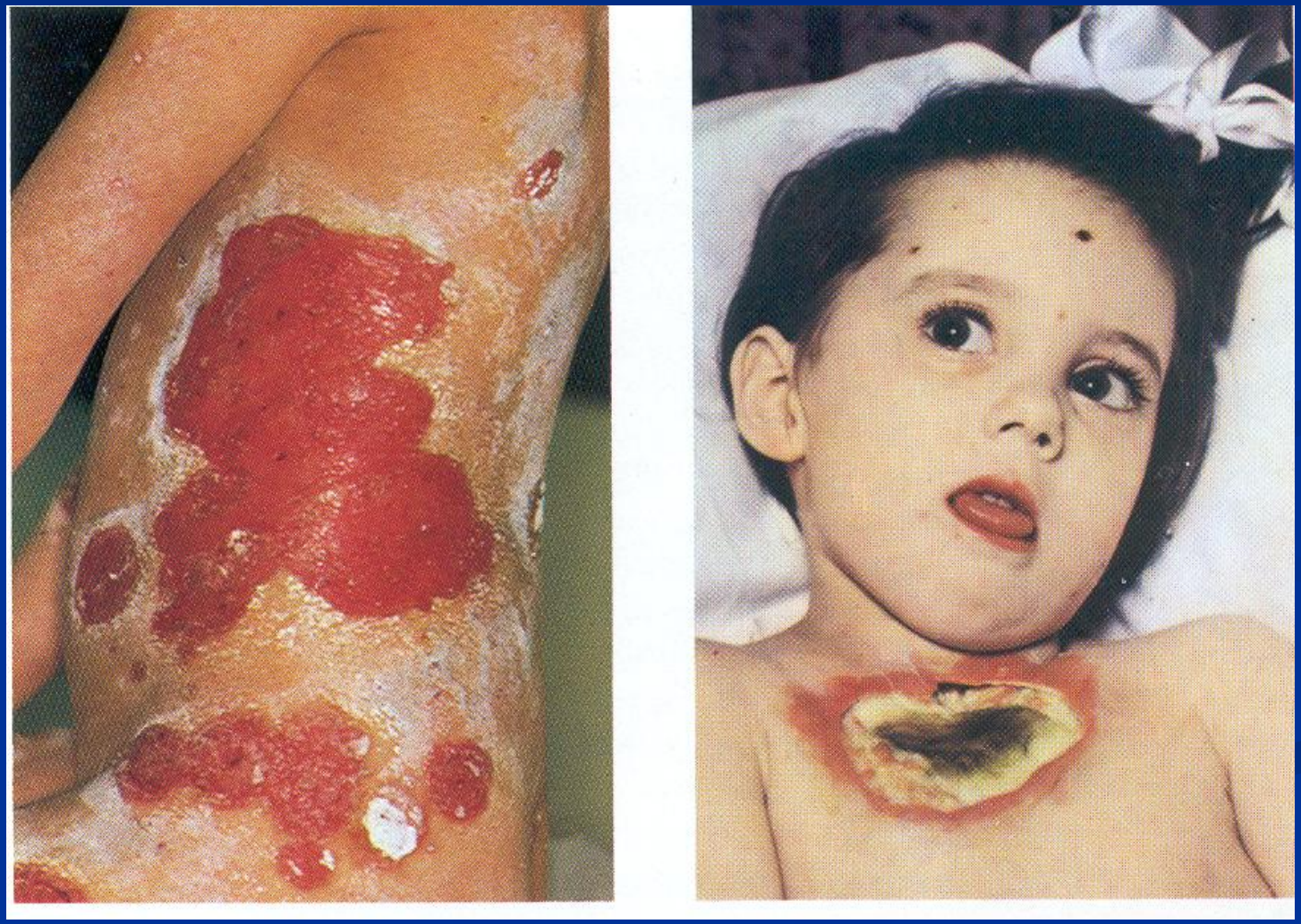




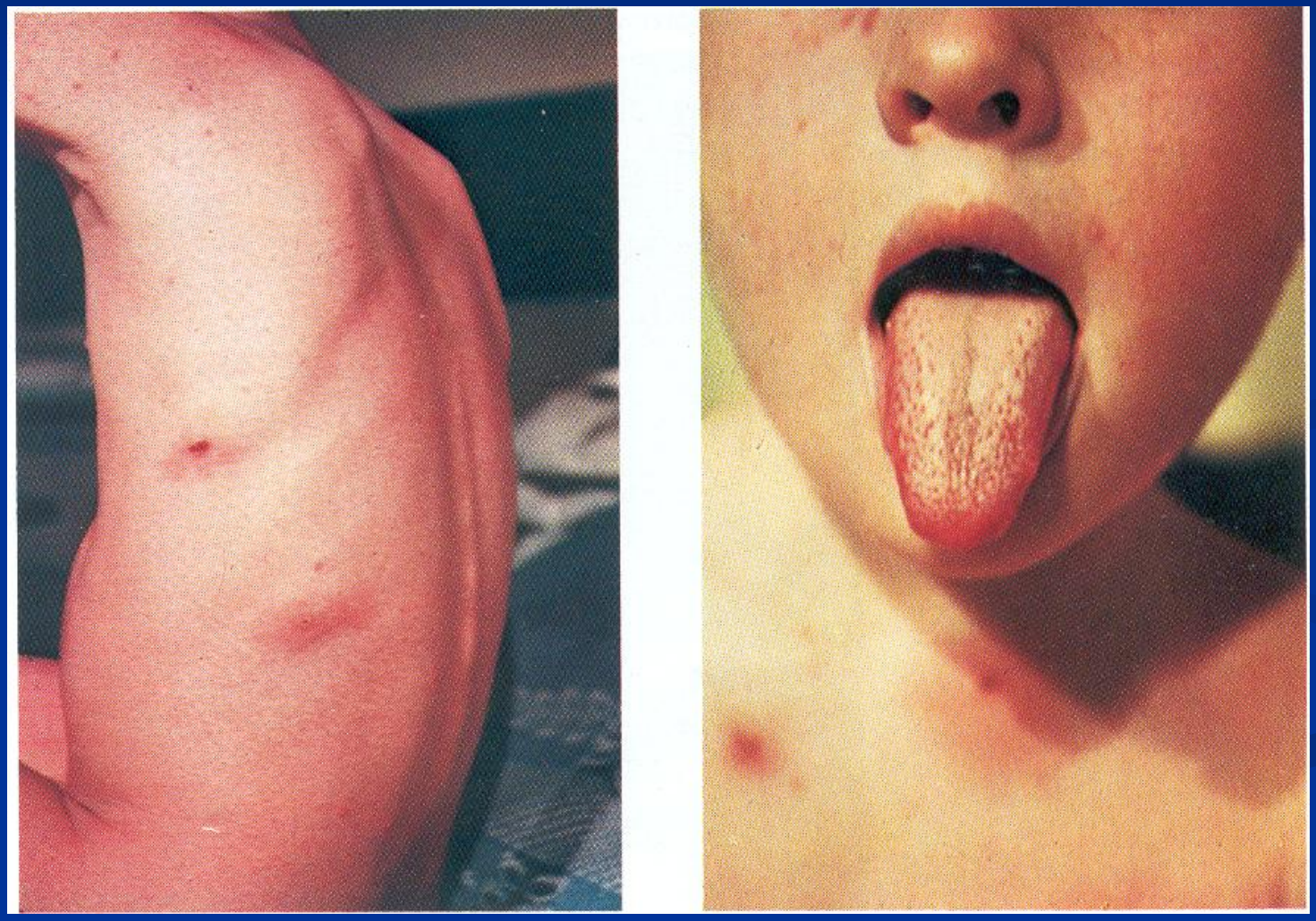
Varicellás hólyagok a garatban és a nyelven



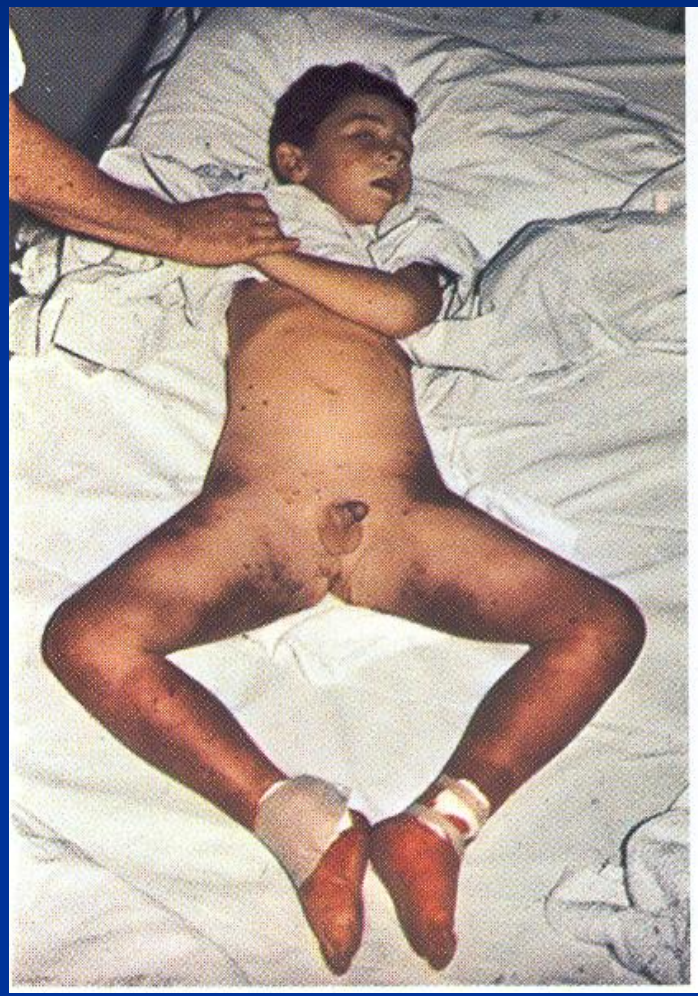
Másodlagos bakteriális fertőzés

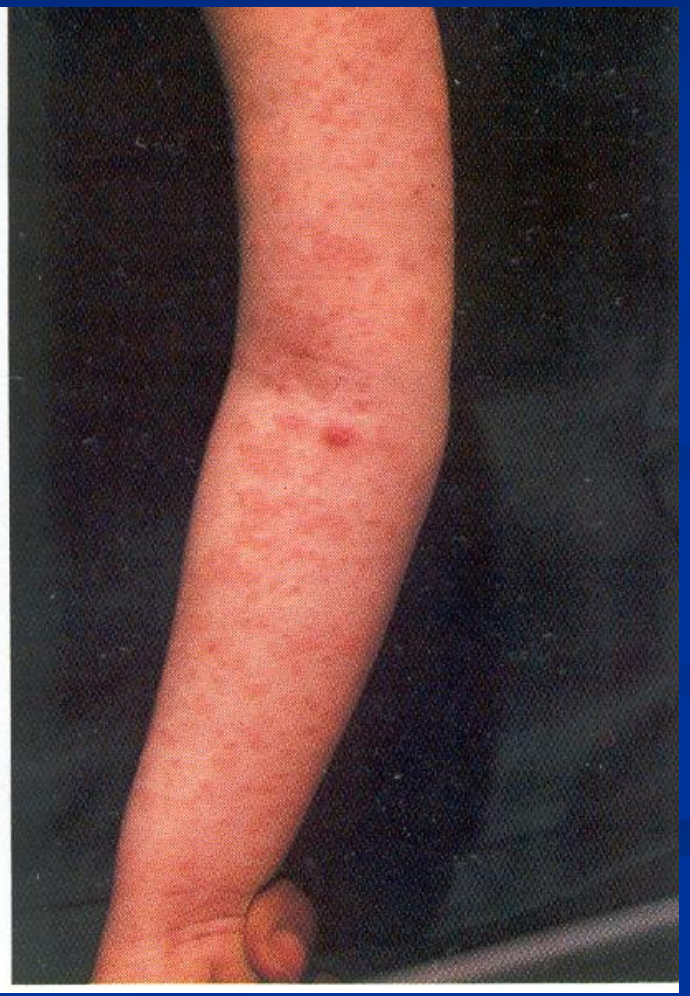


Varicellához társult scarlát

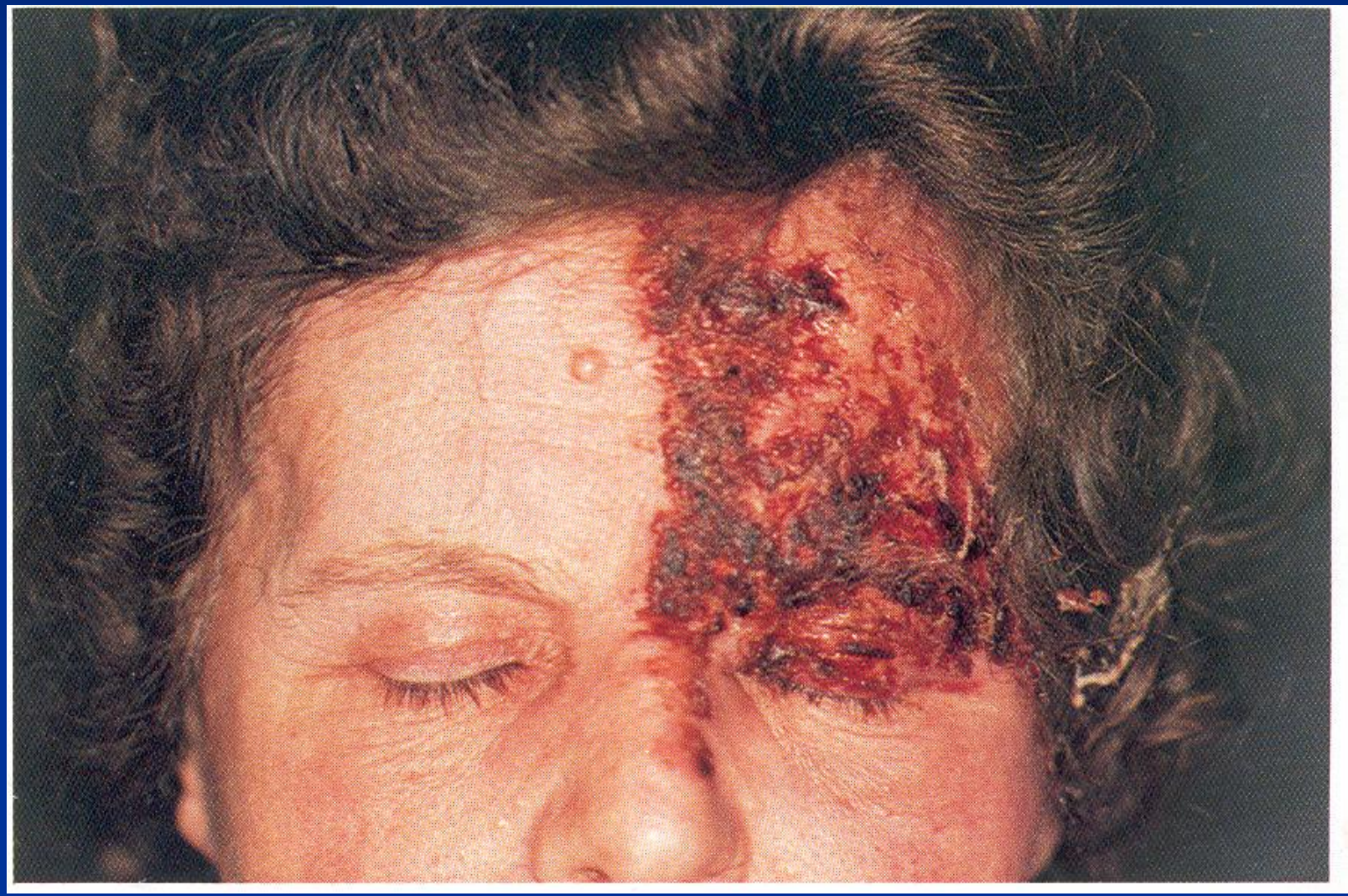


Haemorrhagiás varicella

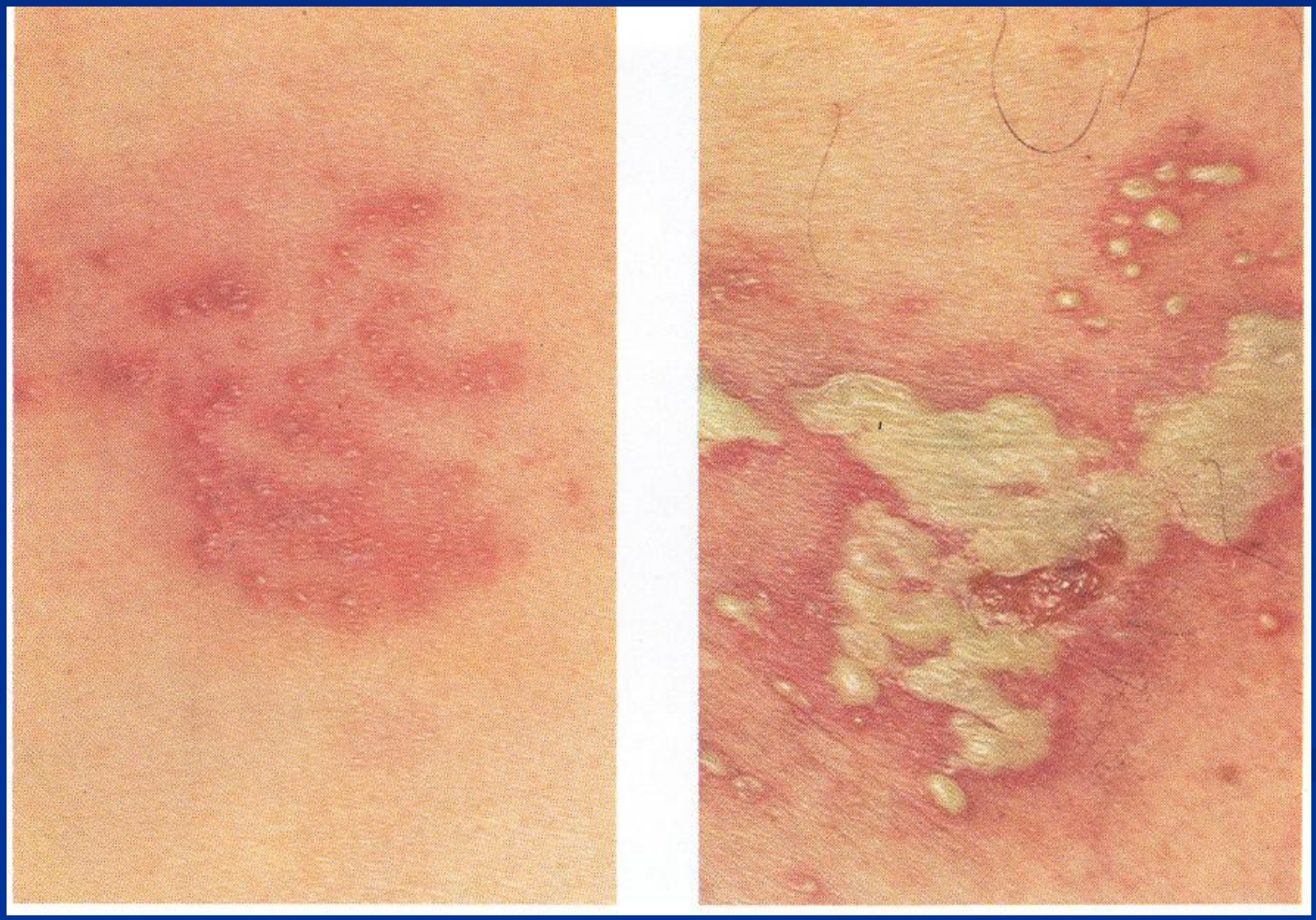




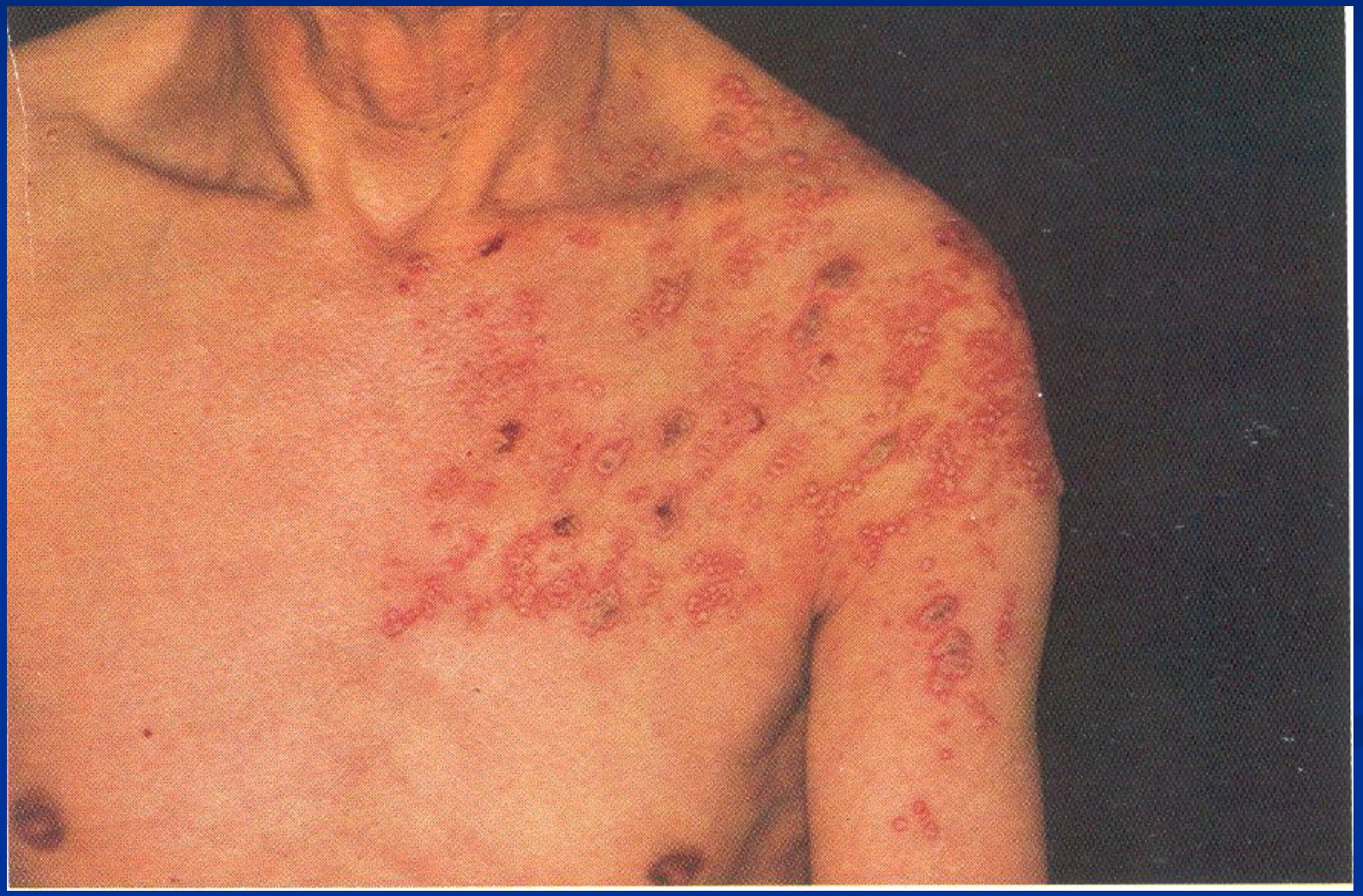
Herpes zoster



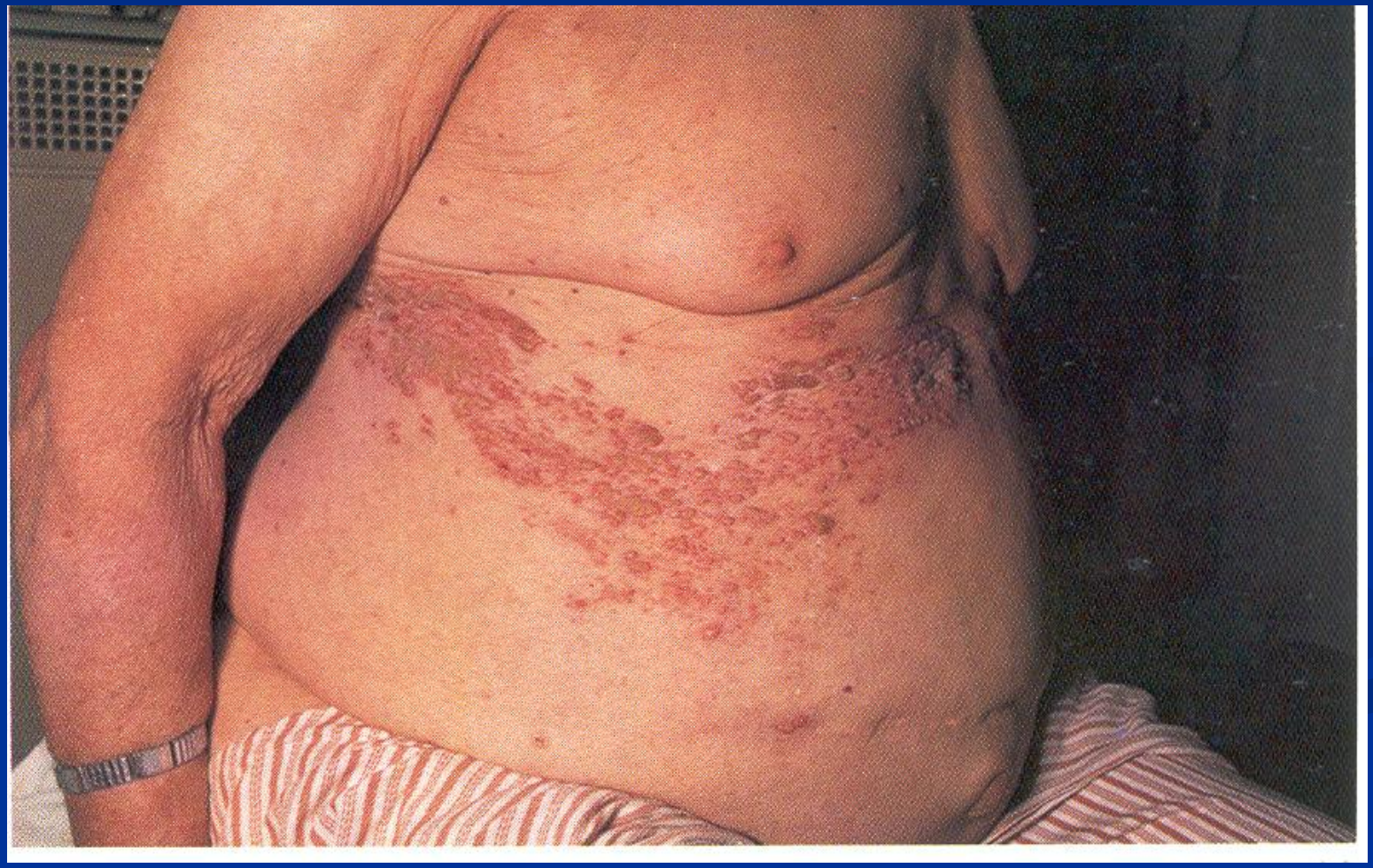
Herpes zosteres elváltozások közelről



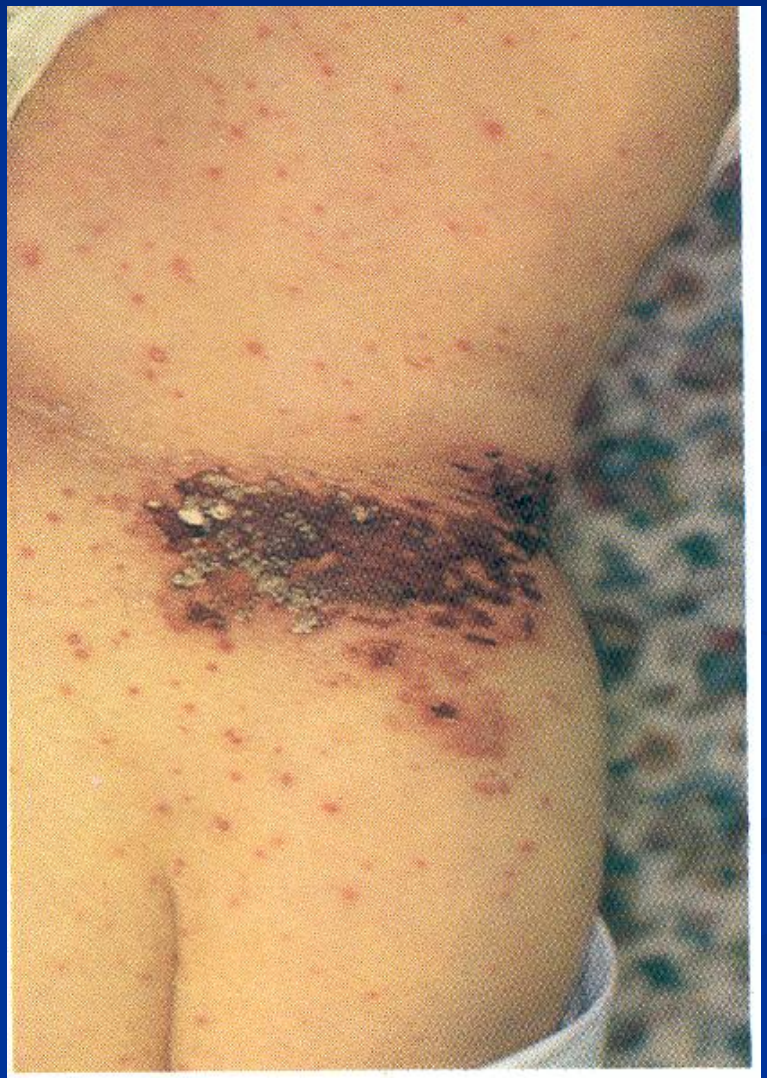
Herpes zoster



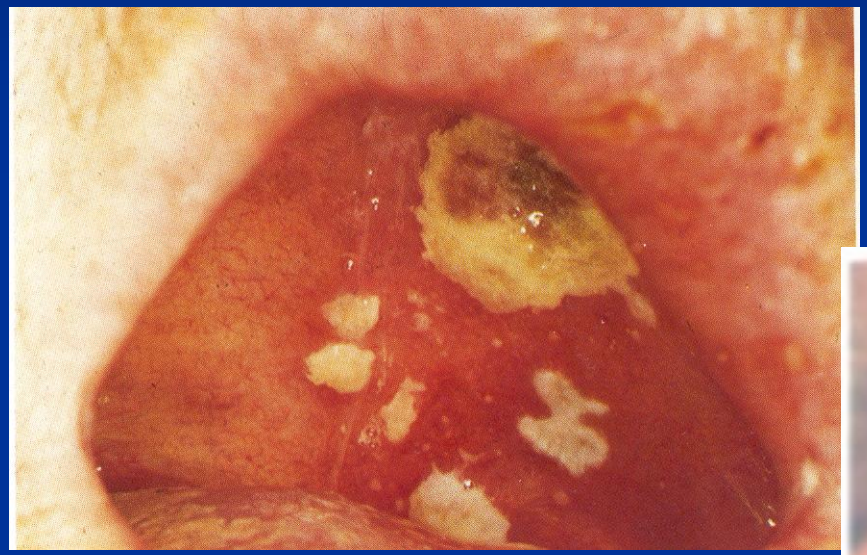
Herpes zoster

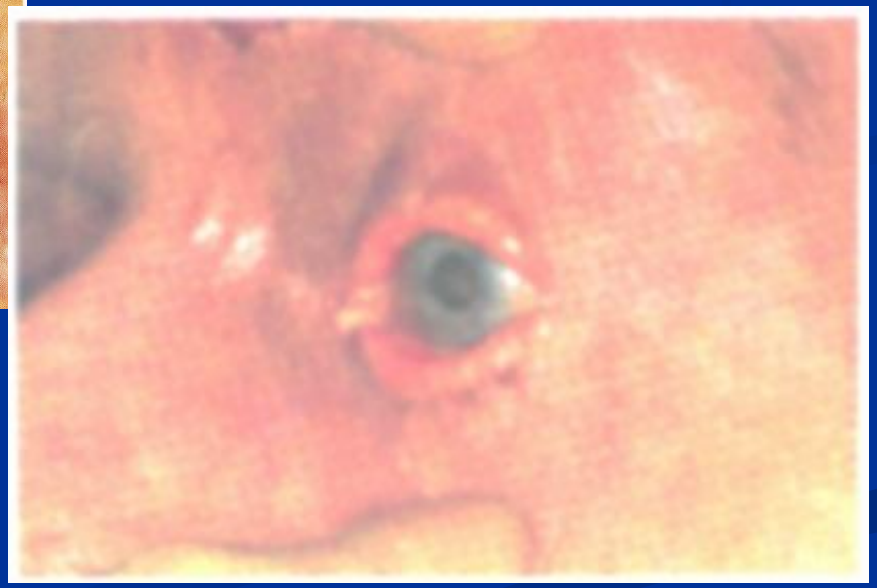


Herpes zoster és varicella együttes előfordulása immuncompromised betegben

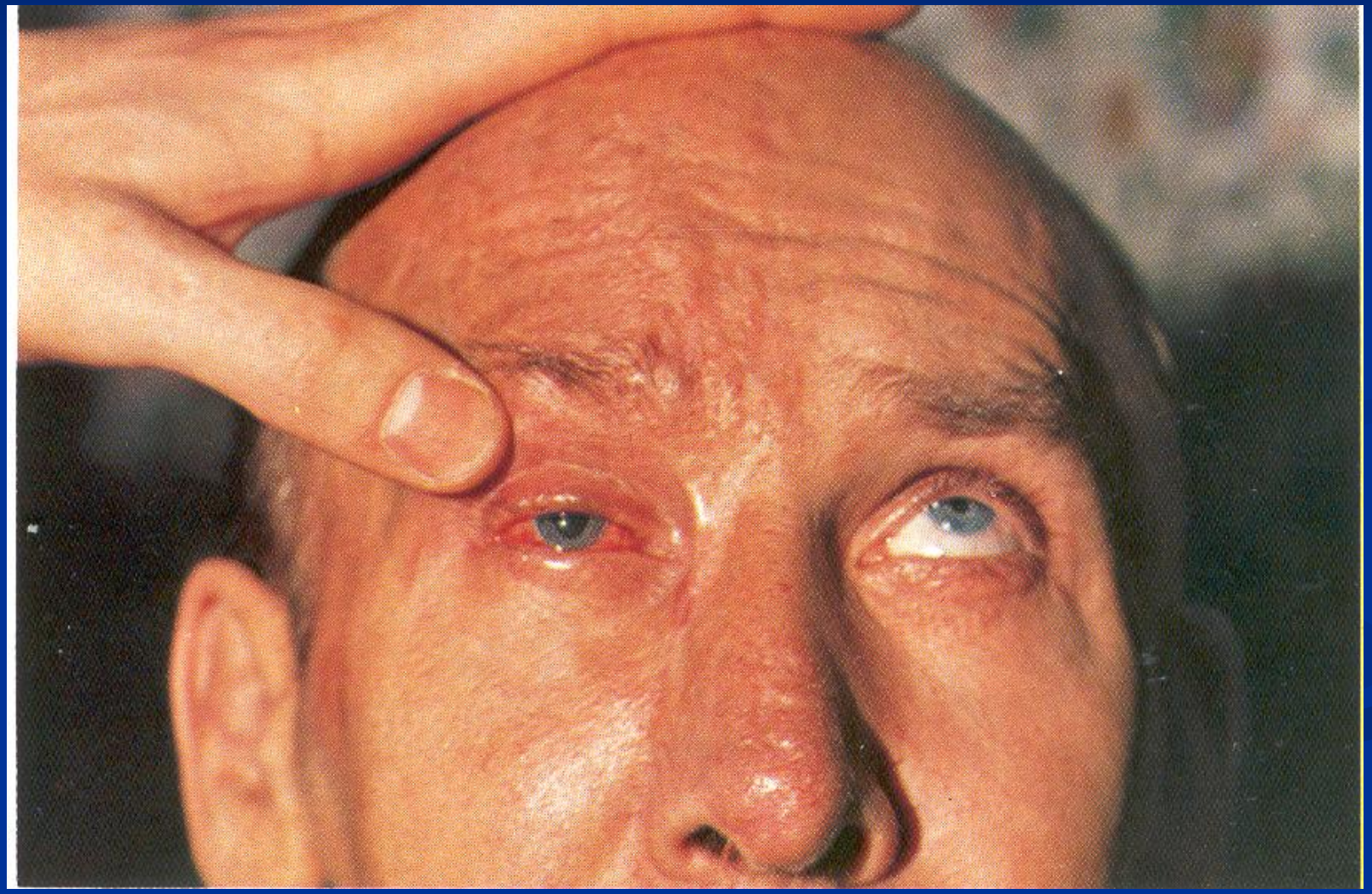


Herpes zosteres elváltozás a pharynxban és a szemen

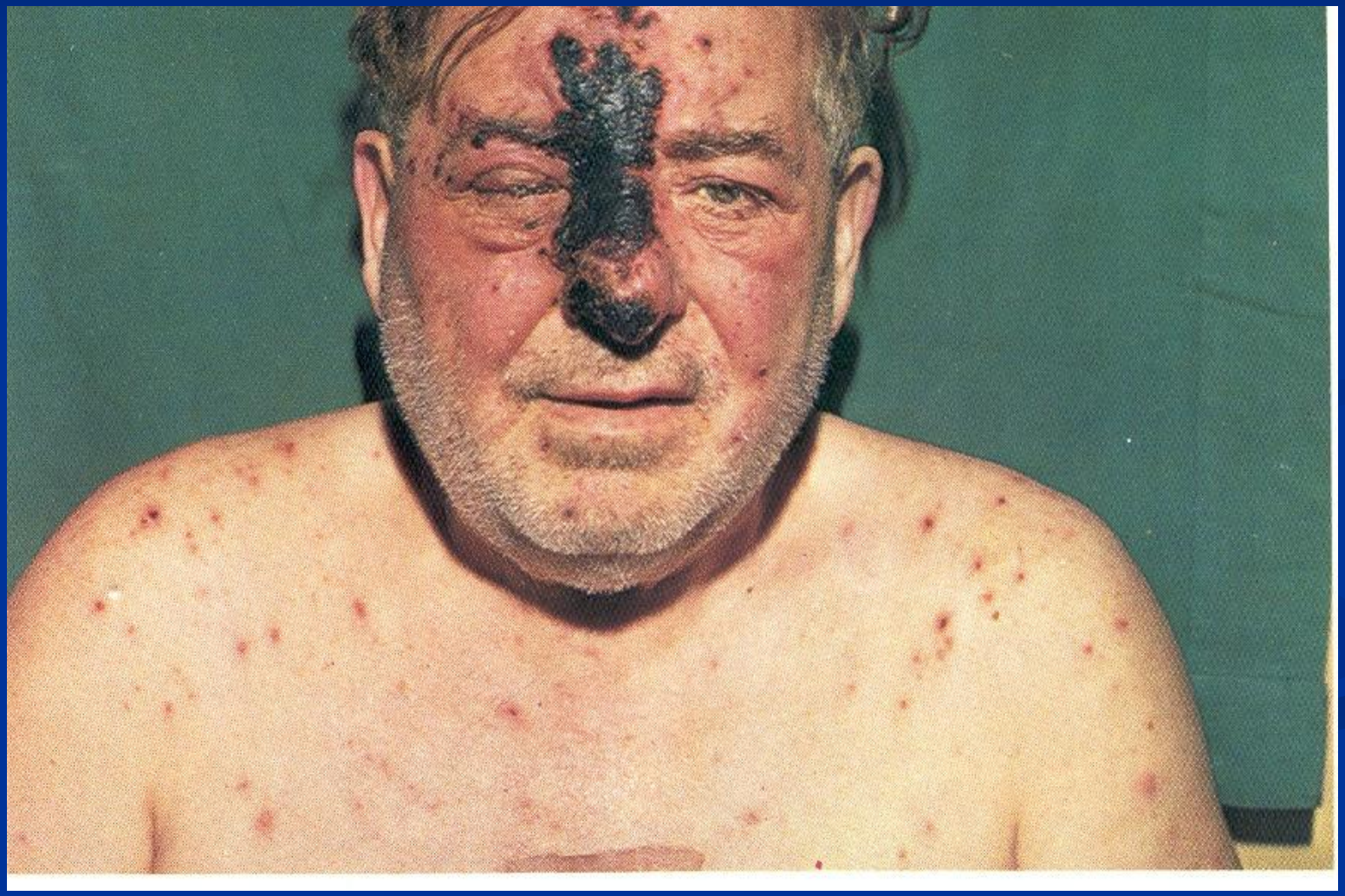




Ophtalmoplegia herpes zoster következtében



Herpes zoster és varicella együttes előfordulása



Herpes zoster és varicella együttes előfordulása