Lesions of oral mucosa in infectious diseases (tonsillitis, diphtheria, herpes infections)

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Diphtheria

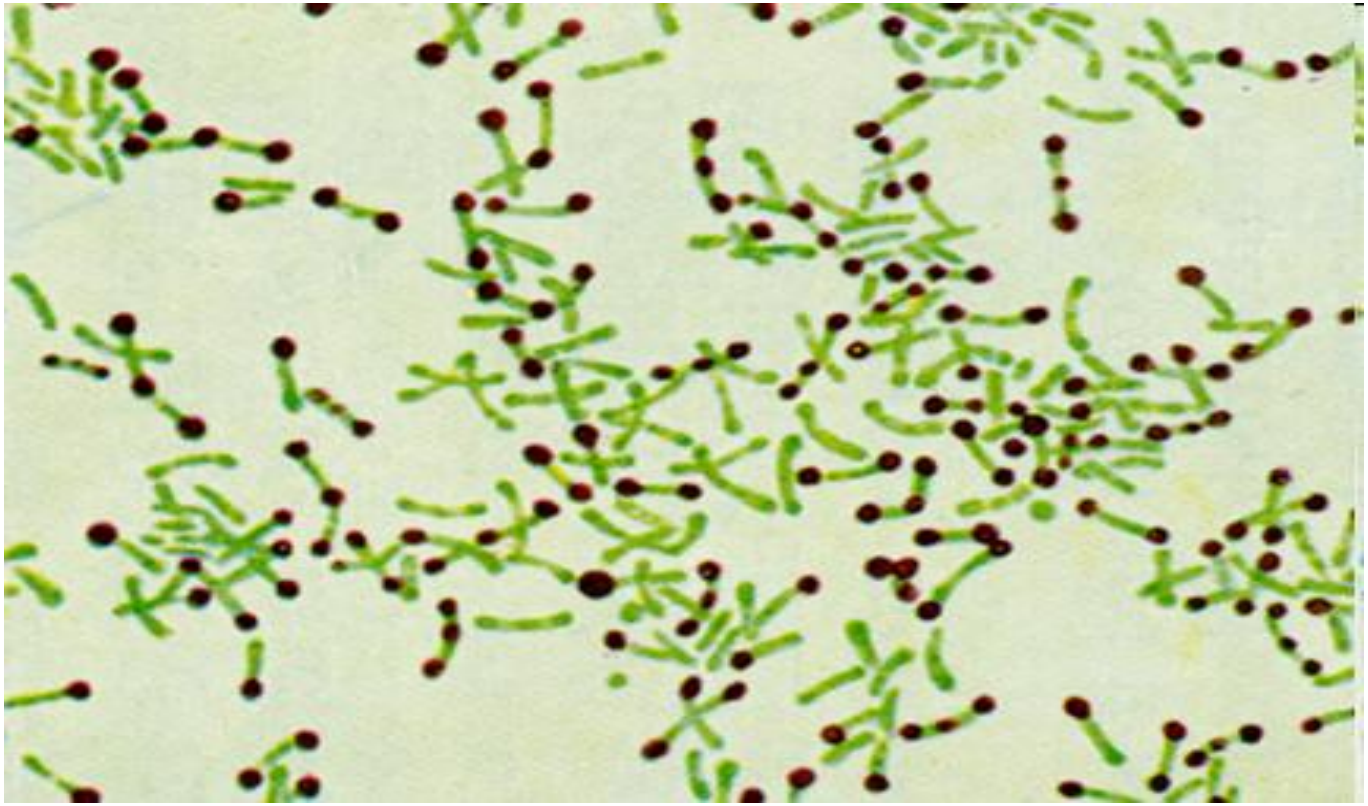
- Diphtheria is an upper respiratory tract illness characterized by sore throat, low fever, and an adherent membrane (called a pseudomembrane on the tonsils, pharynx, and/or nasal cavity.
- Diphtheria toxin produced by C. diphtheriae, can cause myocarditis, polyneuritis, and other systemic toxic effects. A milder form of diphtheria can be restricted to the skin.

Corynebacterium diphtheriae

- Corynebacteria are Gram-positive, aerobic, nonmotile, rod-shaped bacteria classified as Actinobacteria. Corynebacteria are related phylogenetically to mycobacteria and actinomycetes. They do not form spores or branch as do the actinomycetes, but they have the characteristic of forming irregular, club-shaped or V-shaped arrangements in normal growth. They undergo snapping movements just after cell division, which brings them into characteristic forms resembling Chinese letters or palisades.

- The genus Corynebacterium consists of a diverse group of bacteria including animal and plant pathogens, as well as saprophytes. Some corynebacteria are part of the normal flora of humans, finding a suitable niche in virtually every anatomic site, especially the skin and nares. The best known and most widely studied species is Corynebacterium diphtheriae, the causal agent of the disease diphtheria.

Corynebacterium diphtheriae



Stained Corynebacterium cells

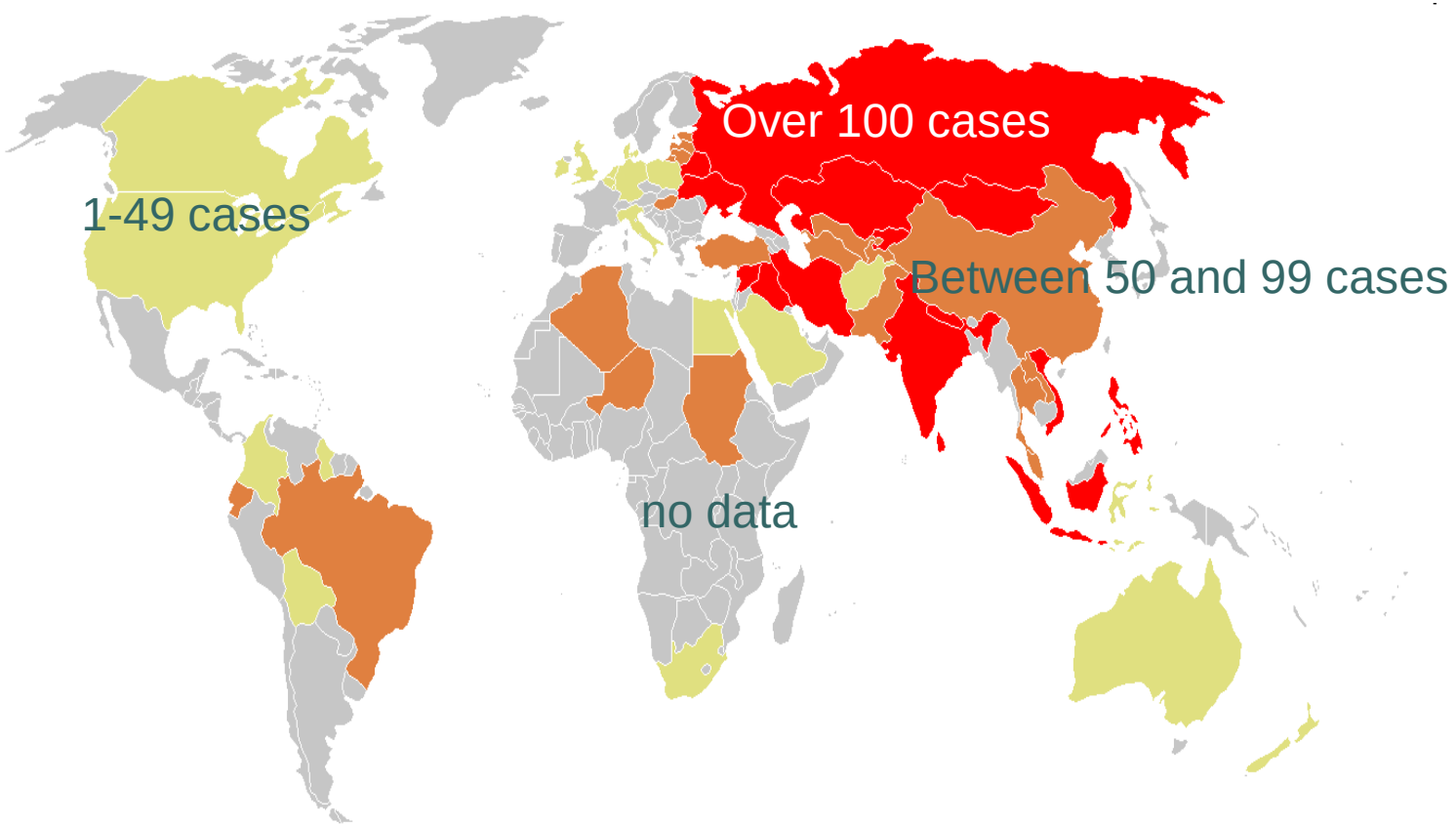
Epidemiology

- Diphtheria is a contagious disease spread by direct physical contact or breathing aerosolized secretions of infected individuals. Once quite common, diphtheria has largely been eradicated in developed nations through wide-spread use of the DPT vaccine.
- For example, in the U.S., between 1980 and 2004 there were 57 reported cases of diphtheria. However, it remains somewhat of a problem worldwide (3,978 reported cases to WHO in 2006) in the face of efforts to achieve global vaccination coverage.

Epidemiology

- Diphtheria is a serious disease, with fatality rates between 5% and 10%. In children under 5 years and adults over 40 years, the fatality rate may be as much as 20%. Outbreaks, although very rare, still occur worldwide, even in developed nations.
- Following the breakup of the former Soviet Union in the late 1980s, vaccination rates in the constituent countries fell so low that there was a surge in diphtheria cases. In 1991 there were 2,000 cases of diphtheria in the USSR.
- By 1998, according to Red Cross estimates, there were as many as 200,000 cases in the Commonwealth of Independent States, with 5,000 deaths.

Epidemiology



Diphtheria cases reported to the World Health Organization between 1997 and 2006

Pathogenicity

- The pathogenicity of Corynebacterium diphtheriae includes two distinct phenomena:

1. **Invasion** of the local tissues of the throat, which requires colonization and subsequent bacterial proliferation. Little is known about the adherence mechanisms of C. diphtheriae, but the bacteria produce several types of pili. The diphtheria toxin, as well, may be involved in colonization of the throat.

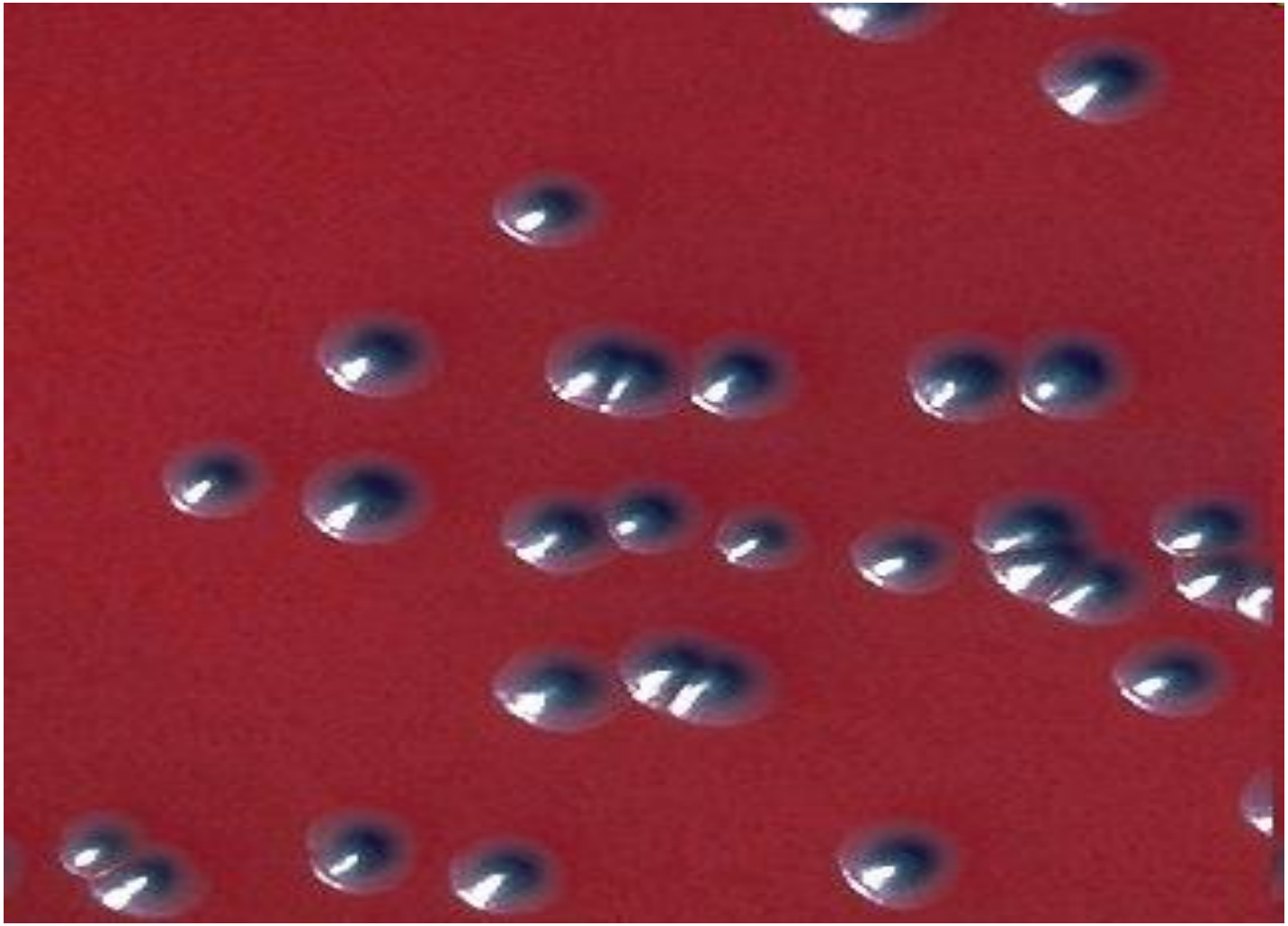
2. **Toxigenesis**: bacterial production of the toxin. The diphtheria toxin causes the death eucaryotic cells and tissues by inhibition protein synthesis in the cells. Although the toxin is responsible for the lethal symptoms of the disease, the virulence of C. diphtheriae cannot be attributed to toxigenicity alone, since a distinct invasive phase apparently precedes toxigenesis. However, it has not been ruled out that the diphtheria toxin plays an essential role in the colonization process due to short-range effects at the colonization site.

Pathogenicity

- Three strains of Corynebacterium diphtheriae are recognized, **gravis, intermedius** and **mitis.**
- They are listed here by falling order of the severity of the disease that they produce in humans. All strains produce the identical toxin and are capable of colonizing the throat.
- The differences in virulence between the three strains can be explained by their differing abilities to produce the toxin in rate and quantity, and by their differing growth rates.

Pathogenicity

- The gravis strain has a generation time (in vitro) of 60 minutes; the intermedius strain has a generation time of about 100 minutes; and the mitis stain has a generation time of about 180 minutes.
- The faster growing strains typically produce a larger colony on most growth media. In the throat (in vivo), a faster growth rate may allow the organism to deplete the local iron supply more rapidly in the invaded tissues, thereby allowing earlier or greater production of the diphtheria toxin.
- Also, if the kinetics of toxin production follow the kinetics of bacterial growth, the faster growing variety would achieve an effective level of toxin before the slow growing varieties.



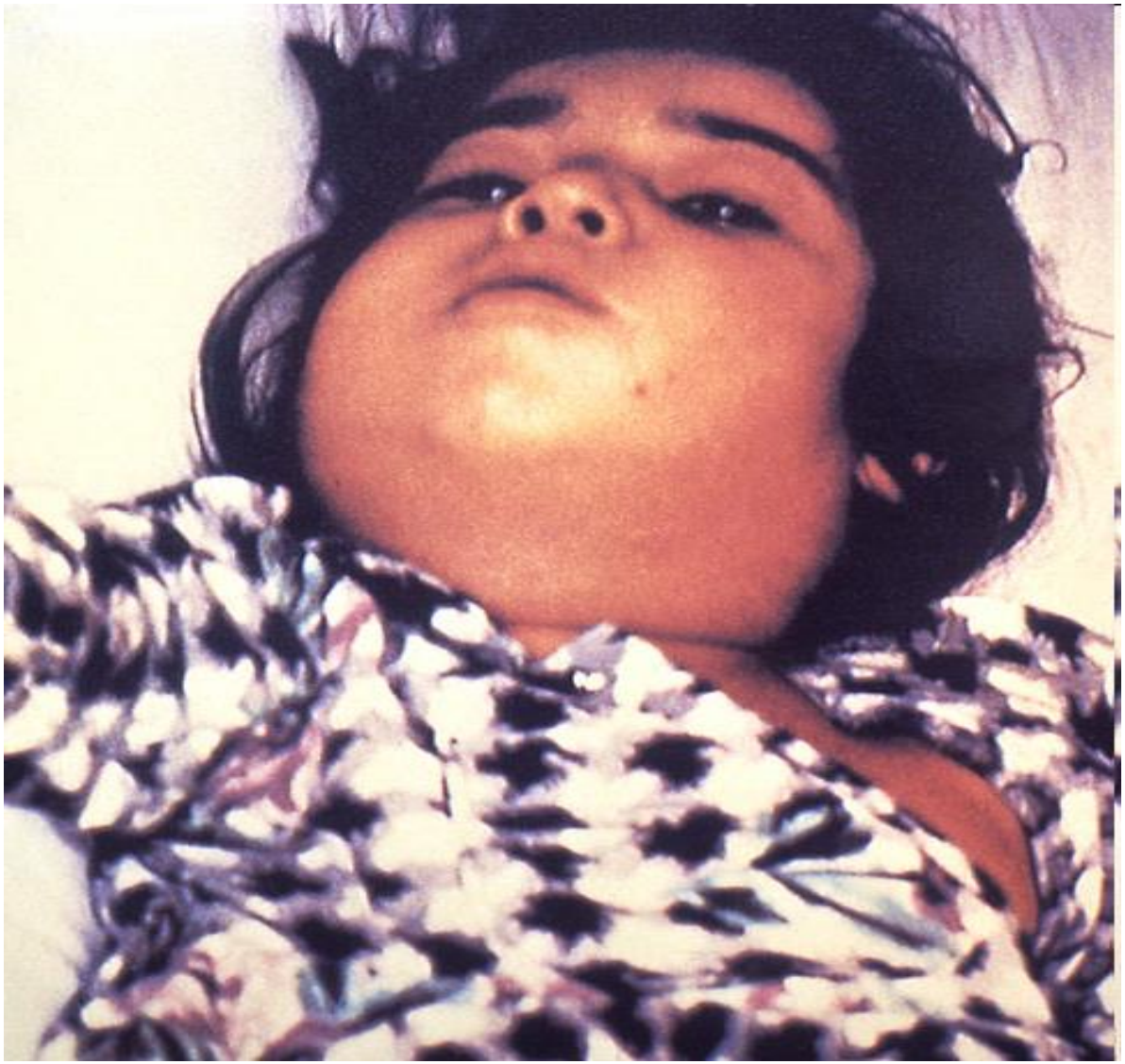
Corynebacterium diphtheriae colonies on blood agar.

Symptoms of diphtheria

The symptoms of diphtheria usually begin two to seven days after patient become infected.

Symptoms of diphtheria can include:

- high temperature (fever) of 38ºC (100.4ºF) or above
- chills
- fatigue (extreme tiredness)
- sore throat
- hoarse voice
- cough
- headache
- difficulty swallowing or pain when swallowing
- difficulty breathing
- foul-smelling, bloodstained nasal discharge
- swollen glands (nodes) in the neck



This child with diphtheria presented with a characteristic swollen neck, sometimes referred to as “bull neck

Symptoms of diphtheria

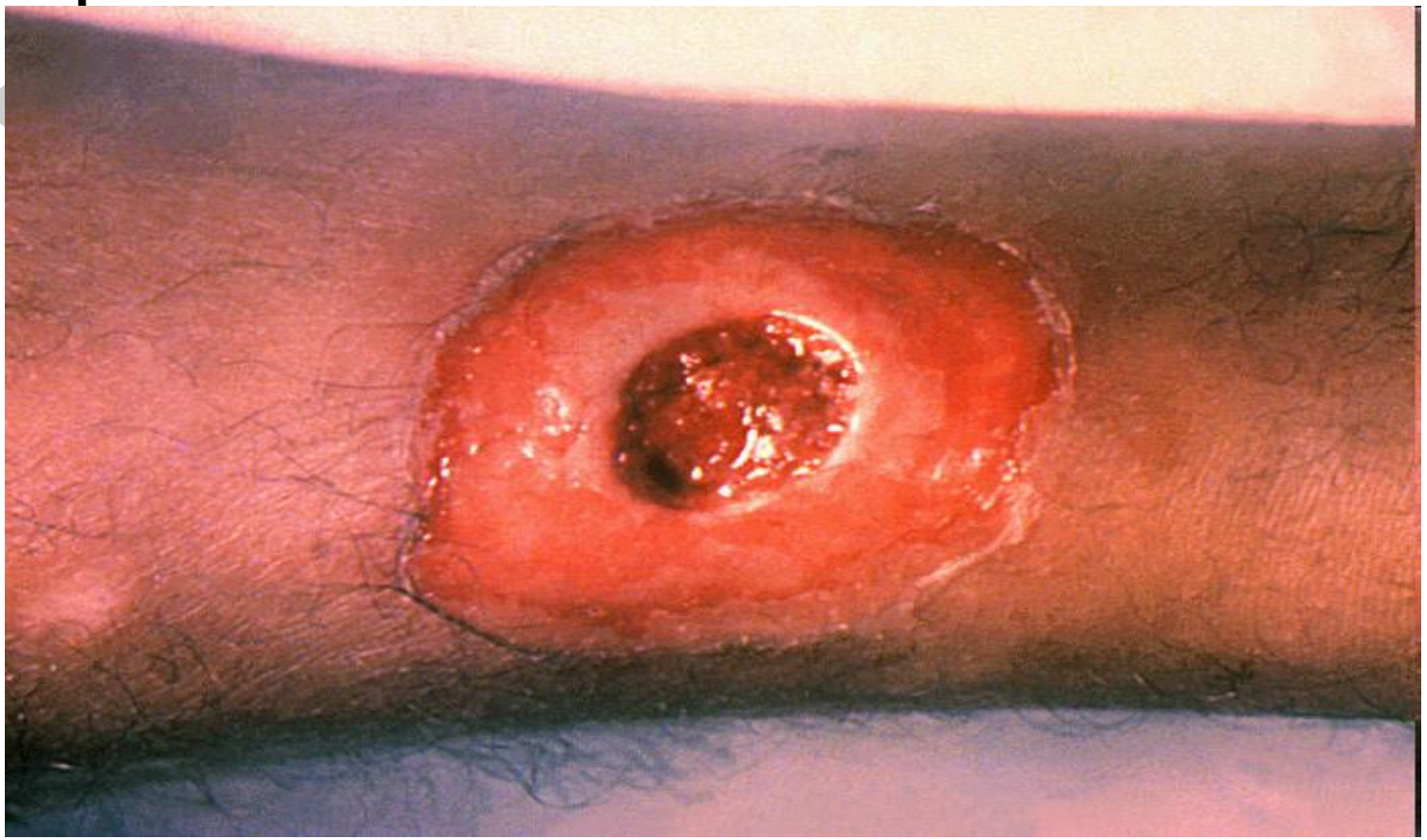
- If patient has diphtheria, a grey-white membrane can develop inside his throat.
- It covers the back of your throat and tonsils and can obstruct breathing.
- The membrane will bleed if you try to remove it.

Symptoms of diphtheria

Diphtheria that affects the skin

- Diphtheria can occasionally affect the skin rather than the throat. This is known as cutaneous diphtheria.

- If you have cutaneous diphtheria, you will develop pus-filled spots on your skin, usually on your legs, feet and hands.
- These blisters and spots will form into a large ulcer surrounded by a red patch of discoloured, sore-looking skin. The ulcer usually heals within two to three months, but it's likely to leave a scar.



A diphtheria skin lesion on the leg

Symptoms of diphtheria

Asymptomatic diphtheria

- People who have been vaccinated against diphtheria won't develop any symptoms if they become infected (asymptomatic diphtheria). However, it's still possible for these people to spread the infection to others.

Diagnosis

- The current definition of diphtheria is based on both **laboratory and clinical criteria**.

Diagnosis

Laboratory criteria

- Isolation of Corynebacterium diphtheriae from a gram stain or throat culture from a clinical specimen, or
- Histopathologic diagnosis of diphtheria by a stain called "Albert's Stain".

Diagnosis

Clinical criteria

- Upper respiratory tract illness with sore throat
- Low-grade fever (>102 °F (39 °C) is rare)
- An adherent true membrane on the tonsil(s),which may extend to pillars, palate and pharynx (post. pharangeal wall).

Treatment

- The disease may remain manageable, but in more severe cases, lymph nodes in the neck may swell, and breathing and swallowing will be more difficult. People in this stage should seek immediate medical attention, as obstruction in the throat may require intubation or a tracheotomy.
- Abnormal cardiac rhythms can occur early in the course of the illness or weeks later, and can lead to heart failure. Diphtheria can also cause paralysis in the eye, neck, throat, or respiratory muscles.

Treatment

- Patients with severe cases will be put in a hospital intensive care unit and be given a **diphtheria antitoxin**.
- Since antitoxin does not neutralize toxin that is already bound to tissues, delaying its administration is associated with an increase in mortality risk.
- Therefore, the decision to administer diphtheria antitoxin is based on clinical diagnosis, and should not await laboratory confirmation

Treatment

- Antibiotics have not been demonstrated to affect healing of local infection in diphtheria patients treated with antitoxin.
- Antibiotics are used in patients or carriers to eradicate C. diphtheriae and prevent its transmission to others.
- **Metronidazole**
- **Erythromycin** (orally or by injection) for 14 days (40 mg/kg per day with a maximum of 2 g/d), or
- **Procaine penicillin G** given intramuscularly for 14 days (300,000 U/d for patients weighing <10 kg and 600,000 U/d for those weighing >10 kg). Patients with allergies to penicillin G or erythromycin can use **rifampin or clindamycin**.

Treatment

- In cases that progress beyond a throat infection, diphtheria toxin spreads through the blood and can lead to potentially life-threatening complications that affect other organs, such as the heart and kidneys.
- The toxin can cause damage to the heart that affects its ability to pump blood or the kidneys' ability to clear wastes. It can also cause nerve damage, eventually leading to paralysis. About 40% to 50% of those left untreated can die.

Complications

- Most complications of diphtheria, including death, are attributable to effects of the toxin.

The severity of the disease and complications are generally related to the extent of local disease.

The toxin, when absorbed, affects organs

and tissues distant from the site of invasion.

The most frequent complications of diphtheria are myocarditis and neuritis.

Complications

- **Myocarditis** may present as abnormal cardiac rhythms and can occur early in the course of the illness or weeks later, and can lead to heart failure. If myocarditis occurs early, it is often fatal.

Complications

- **Neuritis** most often affects motor nerves and usually resolves completely.
- **Paralysis of the soft palate** is most frequent during the third week of illness.
- **Paralysis of eye muscles**, **limbs**, and **diaphragm** can occur after the fifth week.
- **Secondary pneumonia** and respiratory failure may result from diaphragmatic paralysis.

Complications

- Other complications include otitis media and respiratory insufficiency due to airway obstruction, especially in infants.

Vaccination Schedule and Use

- DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine) is the vaccine of choice for children 6 weeks through 6 years of age.
- The usual schedule is a primary series of 4 doses at 2,4,6, and 15–18 months of age.
- The first, second, and third doses of DTaP should be separated by a minimum of 4 weeks.
- The fourth dose should follow the third dose by no less than 6 months, and should not be administered before 12 months of age.

Vaccination Schedule and Use

- If a child has a valid contraindication to pertussis vaccine, pediatric DT should be used to complete the vaccination series.
- If the child was younger than 12 months old when the first dose of DT was administered (as DTP, DTaP, or DT), the child should receive a total of four primary DT doses.
- If the child was 12 months of age or older at the time the first dose of DT was administered, three doses (third dose 6–12 months after the second) completes the primary DT series.

Vaccination Schedule and Use

- If the fourth dose of DT, DTP or DTaP is administered before the fourth birthday, a booster (fifth) dose is recommended at 4 through 6 years of age.
- The fifth dose is not required if the fourth dose was given on or after the fourth birthday.

Vaccination Schedule and Use

- Because of waning antitoxin titers, most persons have antitoxin levels below the optimal level 10 years after the last dose.
- Tetanus toxoid should be given with diphtheria toxoid as Td every 10 years.
- The first booster dose may be given at 11 or 12 years of age. ACIP recommends this dose be administered as Tdap.
- If a dose is given sooner as part of wound management, the next booster is not needed for 10 years thereafter.
- More frequent boosters are not indicated and have been reported to result in an increased incidence and severity of local adverse reactions.

Vaccination Schedule and Use

- Td is the vaccine of choice for children 7 years and older and for adults.
- A primary series is three or four doses, depending on whether the person has received prior doses of diphtheria-containing vaccine and the age these doses were administered.
- The number of doses recommended for children who received one or more doses of DTP, DTaP, or DT before age 7 years is discussed above.

Vaccination Schedule and Use

- For unvaccinated persons 7 years and older (including persons who cannot document prior vaccination), the primary series is three doses.
- The first two doses should be separated by at least 4 weeks, and the third dose given 6 to 12 months after the second. ACIP recommends that one of these doses (preferably the first) be administered as Tdap.
- A booster dose of Td should be given every 10 years. Tdap is approved for a single dose at this time (i.e., it should not be used for all the doses of Td in a previously unvaccinated person 7 years or older).