Diphtheria and Unani Treatment: A Review

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Abstract:

Diphtheria outbreaks, though very rare, still occur worldwide, in the developed and developing countries. Diphtheria has high mortality in non-vaccinated populations. Coryne-bacterium diphtheria produce very potent toxin when infected with a bacteriophage that migrates the toxin-encoding genetic elements into bacteria. The R domain binds to a cell surface receptor, permitting the toxin to enter the cell by receptor mediated endocytosis. The toxin elaborated locally induces a dense necrotic coagulum composed of fibrin, leukocytosis, dead respiratory epithelial cells, leading to white-gray brown pseudo membrane; a common cause of death is suffocation after aspiration of membrane. Complications may include myocarditis, inflammation of nerves, kidney problems, and bleeding due to low blood platelets, Diagnosis by isolation of Coryne-bacterium diphtheria from gram stain or throat culture, or histo-pathogic diagnosis. Treatment with metronidazole, erythromycin, procaine penicillin G orally or by injection or rifampin or clindamycin for patients with allergies to penicillin or erythromycin. Prevention by immunization, diphtheria vaccine is on the World Health Organization list of essential medicines, most important needed in the basic health system. Recommendations from the Advisory Committee on Immunization Practices, 2006-2008, published by CDC are useful. Anti-vaccination groups are doing more harm than good to the society.

Keywords: Diphtheria, Pseudo-membrane, Clinical manifestations, Immunization, Vaccination, Herbal Medicine used in treatment of Diphtheria

I. Introduction.

Diphtheria from Greek word diphtheria meaning leather, is an infection caused by the bacterium Corynebacterium diphtheriae. The disease was first described in the 5th century BC by Hippocrates. The bacterium was discovered in 1882 by Edwin Kleb. In 2013, 4,700 cases were officially reported down from nearly 100,000 in 1980. It is believed, however, that about a million cases occurred per year before 1980s.It currently occurs most often in Sub-Sharan Africa, India, and Indonesia. In June 2016, three cases of

diphtheria were reported in Malaysia with one death. In 2013,it resulted in 3,300 deaths down from 8,000 deaths in 1990.In areas where it is still common, children are most affected. It is rare in the developed world due to widespread vaccination. In the United States 57 cases were reported between 1990 and 2004.Death occurs in between 5% and 10% those affected. Outbreaks, though very rare, still occur worldwide, including in developed nations, such as Germany among non-vaccinated children. Clinical manifestations may vary from mild to severe. They start 2 to 5 days after exposure. Clinical symptoms often come on fairly gradually beginning with sore throat and fever. In severe cases a grey or white patch develops in the throat. Complications may include myocarditis, inflammation of nerves, kidney problems, and bleeding due to low blood platelets. Treatment is with antibiotic erythromycin or penicillin G, tracheostomy may be needed in severe cases. Prevention is by diphtheria toxoid, four doses, given with tetanus toxoid and acellular pertussis vaccine, are recommended during childhood. Adults should receive only one booster, and travelers may benefit from a booster at a 5-year interval. The paper reviews the current literature, clinical manifestations, and role of vaccination in prevention of diphtheria.

II. History and Discovery of Diphtheria

Diphtheria is an ancient disease described in the 5th century by Hippocrates. In Spain experienced an outbreak of diphtheria. The year known as“ EL Ano de los Garrotilos”-the year of Strangulations, in history of Spain. During the years 1735 to 1740, New England and Middle Atlantic states were ravaged by a “throat distemper” which from its description was almost certainly diphtheria, and may have caused the death of more than 20% of the entire population under 15 years of age. In 1735, diphtheria epidemic swept through New England. In 1856, Victor

Fig. 1Alexander Yarsin

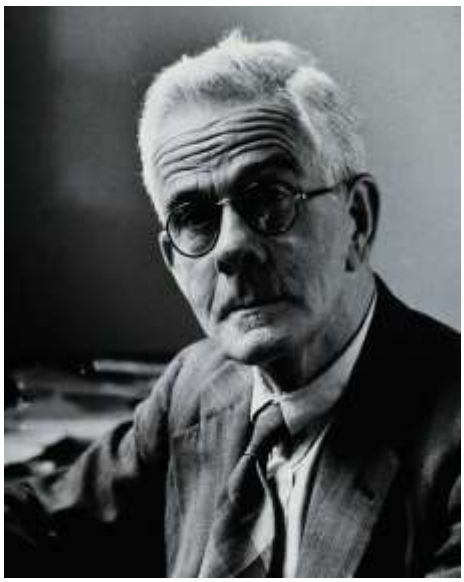

Fig. 2 Alexander Thomas

Fourgeaud described an epidemic of diphtheria in California. In 1883 Edwin Diphtheria: Clinical Manifestations, Diagnosis, And Role Of Immunization In Prevention Klebs identified the bacterium,and in 1884 Loeffler isolated the bacterium. Bacterium was named as Klebs- Loeffler bacterium .Currently bacterium is known as Corynebacterium diphtheriae. Joseph P0'Dwyer

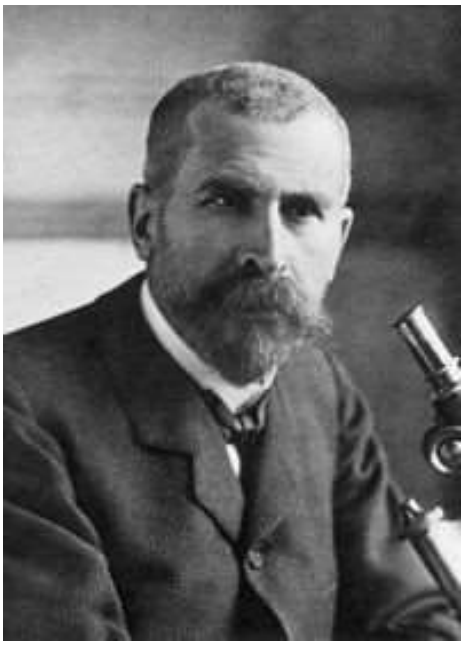

Fig. 3 Emile Roux

Fig. 4 Joseph P0 Dwyer

introduced the 0'Dwyer tube for laryngeal intubation in patients with obstructed larynx in 1885.It soon replaced tracheostomy as the emergency diphtheria intubation method. In 1888, Emile Roux and Alexandre Yersin showed that a substance produced by C. diphtheriae caused symptoms of diphtheria in animals. In 1890. Shibasburo Kitasatto and Emil von Behring immunized guinea pigs with heat-treated diphtheria toxin. The first cure of a person with diphtheria. On Behring won first Nobel Prize in medicine in 1901 for his work on diphtheria. In 1895, HK Mulford Company of Philadelphia started production and testing of diphtheria in the United States. In 1905, Franklin Royer published a paper urging timely treatment for diphtheria and adequate doses of antitoxin. Bela Schick developed Schick test to detect preexistent immunity to diphtheria in an exposed person. A diphtheria vaccine was developed, and deaths began declining in 1924.In 19919,in Dallas,Texas,USA,10 children were killed and 60 others made seriously ill by toxic antitoxin which had passed the tests of the NY State Health Department. Mulford Company (manufacturers) paid damages in every case. In 1920s, there were an estimated 100,000 to 200, 00 cases of diphtheria per year in the United States, causing 13,000 to 15,000 deaths per year. In 1926, Alexander Thomas Glenny increased the effectiveness of diphtheria toxoid by treating it with aluminum salts. In 1974, WHO included DPT vaccine in their expanded program on immunization for developing countries. In 1975, an outbreak of cutaneous diphtheria in Seattle, Washington was reported. In 1994, the Russian Federation saw 39,703 diphtheria cases. In contrast in 1990 there had been only 1,211 cases. In 2010, a case of diphtheria was diagnosed in Port-au-Prince, Haiti after devastating 2010Haiti earthquake. The 15-year old male patient died

while workers searched for antitoxin. In 2013, three children died of diphtheria in Hyderabad India. In 2015, a case of diphtheria was diagnosed in Barcelona, Spain. The 6 years child who died of illness had not been vaccinated due to parental opposition to vaccination. In 2016, a 3 years old girl died of diphtheria in the University Hospital of Antwerp, Belgium. In June,July, 2016, there were 22 diphtheria cases with 5 died of diphtheria in Malaysia.

III. Epidemiology

Infectious Agent Diphtheria is caused by the exotoxin produced by toxigenic strains of the Gram-positive bacterium Corynebacterium diphtheria. Four biotypes exist: mitis, intermedius, gravis, and belfantis. For the bacteria to produce this exotoxin, it must be infected by a virus the coryne bacteriophage containing the gene tox. Nontoxigenic strains of C. diphtheriae rarely cause disease and, when they do, the disease is usually mild and with no systemic complications. Non-toxigenic strains, however, can cause cutaneous diphtheria and have been associated with cases of endocarditis.

Diphtheria was one of the most common causes of morbidity and mortality among children in the pre-vaccine era. Death rates declined with the availability and use of the diphtheria antitoxin and, presumably, other therapeutic measures such as intubation. The incidence of the disease has declined dramatically worldwide with the introduction of active immunization with diphtheria toxoid. However, diphtheria remains endemic in several areas of the world, including some countries of the Caribbean and Latin America. Historically, the disease peaks about every 10 years and outbreaks occur. Most diphtheria cases occur in colder months in temperate climates and in children agedless than 15 years. However, the majority of cases in recent outbreaks, such as a large outbreak in the Russian Federation in the 1990s and cases reported in the United States since 1980, are among persons aged 15 years and older. In tropical areas, the seasonality of the disease is less pronounced, and the cases are milder, with more in apparent, cutaneous, and wound diphtheria cases occurring. Given that C. diphtheriae is ubiquitous and carriers exist worldwide, continuing diphtheria immunization is crucial to keeping this disease under control.

C. diphtheriae is transmitted from person to person via the respiratory tract of a case or transient carrier. Rarely, transmission can occur via contact with skin lesions or fomites. Humans are the only natural host for C. diphtheriae; carriers of the bacterium are there servoir. The incubation period is two to five days after infection with C. diphtheriae.

The period of communicability varies. Transmission can occur as long as the toxigenic bacteria are present in discharge and lesions, which is normally two weeks or less, and seldom longer than four weeks. Antibiotic therapy promptly terminates Diphtheria shedding of the bacilli. There are rare occasions in which chronic carriers shed the bacilli for six months or more.

Even in the pre-vaccine era, diphtheria was rare in infants aged less than 6 months, likely because of the presence of maternal antibodies. Thereafter, most people acquired immunity to diphtheria without experiencing the disease. After receiving three doses of the toxoid, virtually all infants and adults develop diphtheria antitoxin titers considered to be protective. Immunization provides long lasting but not lifelong

immunity, as measured by antitoxin titers. However, some adults who were immunized at a young age can have immunological memory and would be protected if exposed to diphtheria toxin. The protection provided by the toxoid is against systemic disease but not against colonization of the nasopharynx.

Before the Expanded Program on Immunization began in 1977, it is estimated that close to 1 million cases of diphtheria and 50,000–60,000 deaths due to the disease and its complications occurred globally each year. In 2002, only 9,235 cases of diphtheria were reported worldwide. This trend has also been seen in the Region of the Americas. Despite the marked decline in incidence since the widespread use of the toxoid, large outbreaks have occurred, most notably in the 1990s in the countries of the former Soviet Union. This outbreak started in the Russian Federation in 1990, and spread to the Newly Independent States and to Mongolia. Over 150,000 cases and 5,000 deaths were reported between 1990 and 1997. In this outbreak, more cases occurred in young adults than in children. In the Region of the Americas between 1993 and 2004, outbreaks were reported in Colombia, the Dominican Republic, Ecuador, Haiti, and Paraguay. The outbreak in Ecuador, which occurred in 1993–1994, was the largest, with over 500 cases reported. Most cases in these outbreaks occurred in overcrowded and poor areas, and among people with incomplete vaccination or no vaccination history. A shift in the age distribution toward older ages was observed in the outbreak in Ecuador, where half of the cases were among persons aged 15 years or older.

Symptoms of Diphtheria.

Early symptoms of diphtheria may mimic a cold with a sore throat, mild fever, and chills. Usually, the disease causes a thick coating at the back of the throat, which can make it difficult to breathe or swallow. Other body sites besides the throat can also be affected, including the nose, larynx, eye, vagina, and skin.

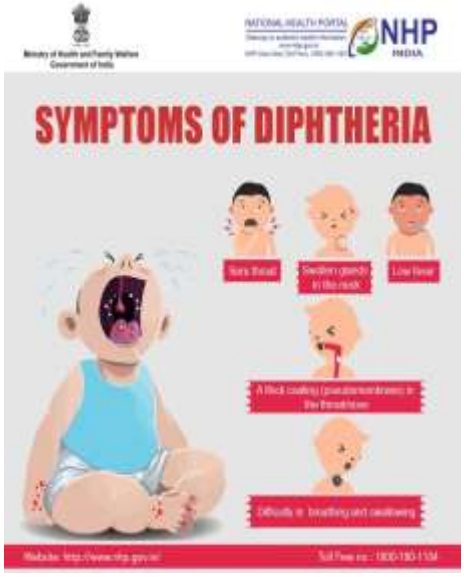

Fig. 5 Symptoms of Diphtheria

Fig. 6 Symptoms of Diphtheria

Diphtheria infection produces symptoms after 2-5 days of acquiring the infection. Although, most individuals are asymptomatic on acquiring the infection, others do exhibit symptoms of common cold. The formation of a thick grey coating on the throat is common sign that differentiates diphtheria over other conditions.

The **common signs and symptoms** of diphtheria include:

- Swollen glands around the face and neck
- Fever
- Chills
- Sore throat
- Intense coughing
- Bluish skin
- Generalized weakness
- Uneasiness and discomfort

The **signs and symptoms advanced stages** of diphtheria infection include:

- Visual disturbances
- Slurred speech
- Difficulty in breathing
- Difficulty in swallowing
- Increased heartbeat
- Pale or skin discoloration
- The signs of cutaneous diphtheria include:
- Pain, redness and swelling of the skin
- Skin ulcers

IV. Clinical Aspects of Diphtheria.

A. Pathogenesis of Diphtheria.

The exotoxin is the main pathogenic factor in the development of diphtheria. As mentioned earlier, only C. diphtheriae infected by a bacteriophage containing the genetox produces the toxin. The toxin produced at the site of the diptheritic membrane is adsorbed into the bloodstream and is responsible for remote manifestations of diphtheria, such as myocarditis, nephritis, and neuritis.

B. Clinical Features of Diphtheria.

Diphtheria usually involves the respiratory tract, but can affect any mucosal membrane. The disease has an insidious onset, with nonspecific mild symptoms and signs; fever is usually low and rarely exceeds

38.5°C. Symptoms and signs are proportional to the amount of toxin. If enough toxins are adsorbed, the patient can appear pale, have a rapid pulse, and become severely prostrated.

C. Classification of Diphtheria

Diphtheria can be classified according to the site of infection:

- **Nasal diphtheria:** This form is characterized by a mucopurulent nasal discharge, which can become blood-tinged, and a white membrane that can form in the nasal septum. Isolated nasal diphtheria is uncommon and usually mild; its diagnosis can easily be missed.
- Pharyngeal and tonsillar diphtheria: This constitutes the "classic" form and concomitant involvement of other sites respiratory or not can occur. At first, the pharynxcan be injected at examination, but soon, small white patches appear and grow, forming a grayish-white adhering membrane that can cover the entire pharynx, Including the tonsils, uvula, and soft palate. Attempts to dislodge the membrane cause bleeding. Edema and inflammation of the surrounding soft tissues and painful enlargement of the anterior cervical lymph nodes can result in the so-called"bull neck," which is indicative of severe infection. Leftun treated, the membrane softens after about a week and gradually sloughs off in pieces or as a single block. Systemic symptoms begin to disappear as the membrane falls off.

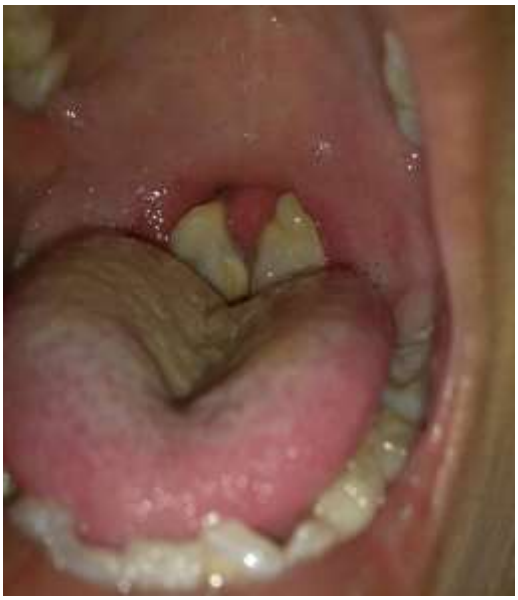

Fig. 7 Pharyngeal l diphtheria

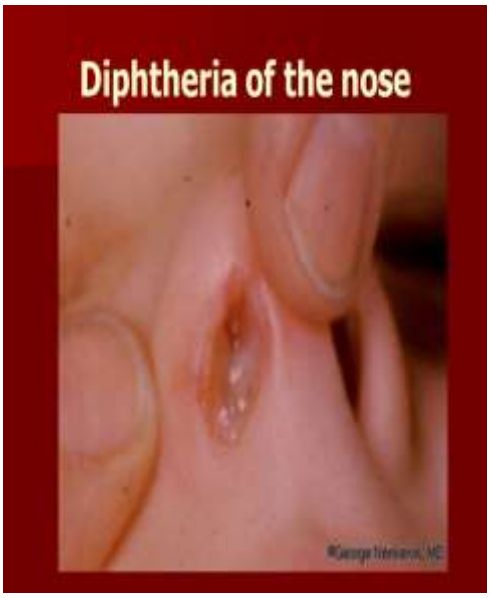

Fig. 8 Nasal diphtheria

- Laryngeal diphtheria: This form can occur in isolation or can be an extension of the pharyngeal form. It is more common in children aged less than 4 years, and presents as gradually progressing hoarseness, barking cough, and stridor. It can lead to pharyngeal obstruction and death.
- Cutaneous diphtheria: This is a mild skin infection that can be caused by toxin-producing or non–toxin-producing bacilli, whereas all other forms of diphtheria are caused by Toxin-producing

organisms. It is more common in the tropics, and has often been associated with poverty and overcrowding. Individuals with cutaneous diphtheria can serveas the source of infection for others.

D. Laboratory Diagnosis

The best samples for bacteriological culture are pharyngeal swabs obtained under direct visualization, preferably from the edge of or directly beneath the membrane. In general, Gram's stains are not recommended as other Corynebacterium species can normally inhabit the throat. After C. diphtheriae has been isolated, the biotype can be determined. To ascertain if the isolated C. diphtheriae is toxigenic, testing for toxin production is usually available only in selected reference laboratories.

E. Differential Diagnosis

The differential diagnosis of diphtheria includes:

- Bacterial and viral pharyngitis;
- Vincent's angina (caused by anaerobic organisms);
- Infectious mononucleosis;
- Oral syphilis;
- Candidiasis.

For laryngeal diphtheria, the differential diagnosis includes epiglottitis caused by:

- Homophiles influenza type b;
- Spasmodic croup;
- The presence of a foreign body;
- Viral laryngo tracheitis.

F. Complications of Diphtheria.

Most complications of diphtheria are due to the release of the toxin, or poison. The most common complications are inflammation of the heart leading to abnormal heart rhythms, and inflammation of the nerves which may cause temporary paralysis of some muscles. If the paralysis affects the diaphragm (the major muscle for breathing), the patient may develop pneumonia or respiratory failure. The thick membrane coating at the back of the throat may cause serious breathing problems, including suffocation.

The severity of the signs and symptoms is usually proportional to the extent of the local inflammation, which is related to the production of the toxin in the diphtheritic membrane. Severe complications include respiratory obstruction, acute systemic toxicity, myocarditis, and neurological complications. Local complications are related to the extension of the membrane:

- Laryngeal diphtheria and aspiration of the membrane can lead to respiratory obstruction;
- If the membrane extends downward, it can result in pneumonia and respiratory obstruction;
- Sinusitis and otitis media are usually associated with nasopharyngeal diphtheria due to edema of the upper respiratory tract. Systemic complications resulting from diphtheria toxin include:

- Myocarditis is the main cause of diphtheria-related mortality. It can be complicated by heart blocks and can progress to congestive heart failure. Early myocarditis occurs between the third and seventh day of infection and is usually fatal. Less severe, late myocarditis usually occurs the second week after onset and, occasionally, later.
- Neurological complications mostly manifest as a toxic peripheral neuropathy that primarily affects the motor nerves. These complications usually begin two to eight weeks weeks after the onset of illness. Paralysis of eye muscles, limbs, and diaphragm can occur after the fifth week. Diaphragmatic paralysis can be serious, causing pneumonia or requiring mechanical ventilation. Normally, these neurological complications resolve completely. The case-fatality rate for non-cutaneous diphtheria is 5% to 10%, and has remained at those levels for the last 50 years. Children aged less than 5 years and persons over 40 years have a higher risk of death.

Untreated diphtheria infection can increase the risk of complications, such as:

- **Breathing problems:** Diphtheria infection produces harmful toxins that affect the other tissues surrounding the nose and throat. The thick grey mass formation obstructs the airway passages, thus making it difficult to breathe.
- **Heart damage:** The diphtheria toxin passes through the bloodstream and causes inflammation of the tissue and organs in the body. When the toxin affects the heart, it causes myocarditis (inflammation of the heart muscle).
- **Nerve damage:** The nerves supplying the throat, arm, feet and respiratory tract may be affected producing the complications.

V. Treatment of Diphtheria.

Prompt recognition and treatment of diphtheria are very important, as the early use of diphtheria antitoxin is associated with a better outcome. Complications are directly proportional to the number of days between the onset of illness and administration of antitoxin. The patient should be isolated. Treatment should be started immediately after taking bacteriological specimens, without waiting for laboratory confirmation.

A. Antitoxin. The use of diphtheria anti-toxin is the centerpiece of diphtheria treatment, and it should be administered when diphtheria is suspected. Antitoxin will neutralize circulating (unbound) toxin, but not toxin already fixed to the tissues. For this reason, the entire therapeutic dose should be administered at one time. The antitoxin can be given intramuscularly or intravenously; therapeutic levels of antitoxinin the blood can be achieved faster with IV. Administration and this method are usually preferred. The dose to be used ranges from20,000 to 120,000 units, depending on the size of the lesions, as the amount of toxin produced depends on the size of the membranes and the interval since the time of onset. Since the antitoxin is produced in horses, some experts suggest testing for hypersensitivity to equine serum. The antitoxin is **not** indicated for prophylaxis.

B. Antibiotics. Patients with diphtheria should also receive antibiotics to eliminate the bacteria and thus reduce the duration of communicability and carriage.

The recommended antibiotics are:

- Procaine penicillin G. It should be administered intramuscularly, at a dose of25,000–50,000 units/kg/day for children and 1.2 million units/day for adults, in two divided doses **or**
- Erythromycin. Parenteral erythromycin (40–50 mg/kg/day, with a maximum of 2 g per day) may be used until the patient can swallow, after which he or she may be given erythromycin orally in four divided doses per day or oral penicillin V (125–250 mg four times per day).Treatment should continue for 14 days. Nonspecific supportive measures are indicated in addition to antitoxin, isolation, and the use of antibiotics. Additionally, initiation or completion of active immunization against diphtheria is recommended for cases during the convalescent period, because disease does not necessarily confer immunity.

VI. Management of Diphtheria.

- **Vaccination.** The diphtheria vaccination status of case contacts should be assessed to complete the primary three doses of diphtheria vaccine in those who need it, give the fourth dose to children who have received the primary series, and give an age-appropriate diphtheria booster if no booster has been given in the previous five years.

  All pregnant women should receive Tdap during each pregnancy, preferably early in the time period between 27 and 36 weeks' gestation. Recent studies show that vaccination during pregnancy reduces ababy's risk of getting pertussis in early infancy by 90percent. Because infants are not adequately protected against pertussis until they have received at least 3doses of DTaP, it is especially important that all contacts (family members, caregivers) of infants younger than age 12 months are vaccinated with Tdap if they haven't previously received Tdap. If a new mother hasn't been vaccinated with Tdap, she should receive it before hospital discharge, even if she is breastfeeding.
- **Antibiotics.** Prophylactic antibiotics are also indicated for contacts: one dose of Benzathine penicillin G, IM (600,000 units for persons aged less than 6years, and 1.2 million units for those aged 6 or older), or 7 to 10 days of oral erythromycin (40 mg/kg/day for children and 1 g/day for adults). If compliance cannot be guaranteed, one dose of Benzathine penicillin is preferred for prophylaxis. If the contact is cultured and the result is positive, he or she should be treated as a case. When feasible, management of close contacts also includes keeping them under surveillance for seven days to detect disease, and taking nose and throat samples for culture before starting antibiotic prophylaxis.

VII. Prevention of Diphtheria.

Diphtheria can be prevented by immunization. The diphtheria vaccine was developed in 1923.It is on the World Health Organization's List of Essential Medicines, the most important needed in a basic health system. It use has resulted in a more than 90% decrease in number of cases globally between 1980 and

2000.Three initial doses are recommended after which it is about 95% effective. It is effective for about 10 years at which time a booster dose is needed. Immunization may start at six weeks of age with further doses given every four weeks. The diphtheria vaccine is very safe, significant side effects are rare. The vaccine is safe in both pregnancy and among those who have poor immune function. The diphtheria vaccine is delivered in several combinations. One includes tetanus toxoid (known as dT or DT vaccine) and other comes with the tetanus and pertussis vaccines, (DPT).The World Health Organization has recommended its use since 1974, and about 84% of world population is vaccinated. Recommendations from the Advisory Committee on Immunization Practices were up-dated in 2006 and 2008, published by CDC include:

- For persons 11 years or more years old a single 0,5ml,Tdap is followed four to eight weeks later by 0.5 ml
- Td. with second dose of Td 6 to 12 months after the first.
- Booster immunization: persons 11 to 18 years old should receive one dose of Tdap and then receive the standard Td booster at 10 years later intervals.
- Those 19 to 64 years old should have their next booster as Tadp, to reduce carriage, clinical illness and transmission of pertussis.

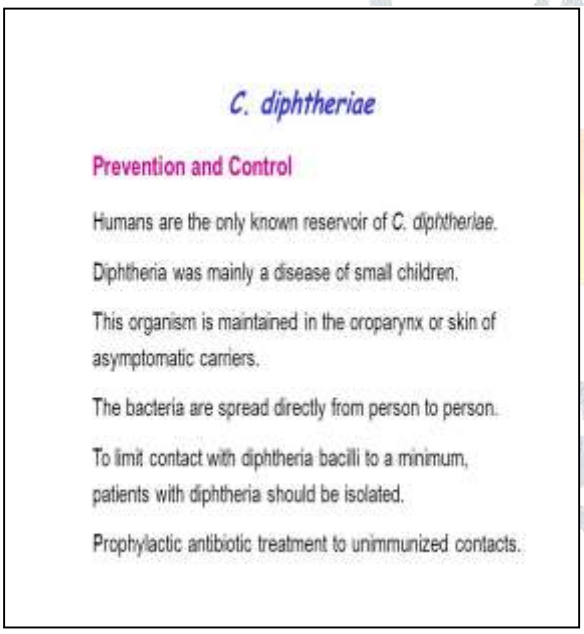

Fig. 9 Prevention of Diphtheria

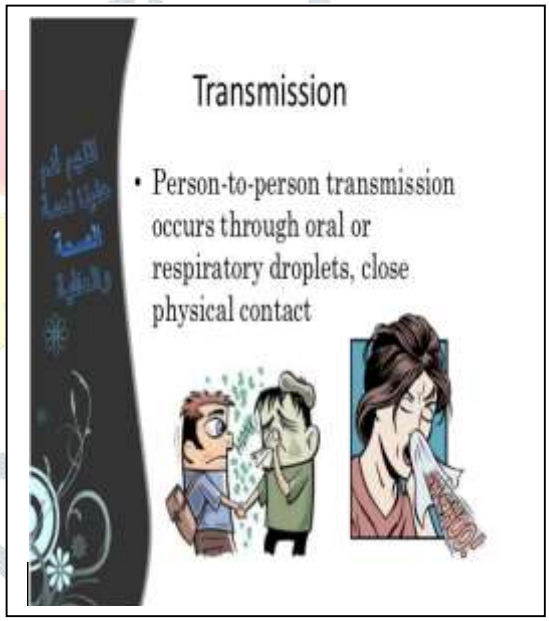

Fig. 10 Prevention of Diphtheria

The treatment for diphtheria requires a compulsory hospital stay to prevent the spread of infection among family and friends. During this period, the patient is isolated from other patients to prevent the spread of infection to other immunized or non-immunized patients. Diphtheria infection can be prevented by spreading awareness about vaccinations. Diphtheria vaccine is administered through single shots, mostly in combination with pertussis and tetanus vaccines. Vaccinating your child for diphtheria infection help prevent

the onset of infection by up to 10 years of age. However, administering a booster dose for every ten years can help in long term prevention of diphtheria.

VIII. Herbal Drugs used in the treatment of Diphtheria.

Seek immediate medical help if you think you or any member of your family has diphtheria. Just like any other disease, treatment is most effective when given early. Treatments for diphtheria include antibiotics and an antitoxin that neutralizes the infection. And here are some home remedies that can help treat this condition effectively.

Garlic: Garlic (or *lahsoon* in Hindi) is an effective home remedy for curing various ailments, including diphtheria. It is said that taking a spoonful of 2-3 crushed garlic cloves can help lower the fever and cure this disease.

Pineapple: Drinking fresh juice of pineapple may help remove the throat deposits, thereby improving the symptoms of this infection. Since pineapple juice contains beta-carotene, it can effectively cure diphtheria.

Basil leaves: The health benefits of basil leaves or Tulsi is well-known. The antibacterial properties in basil leaves can help cure respiratory infections. Drink basil leaves infused water to get relief from diphtheria.

Passionflower: Passionflower is an amazing herb that offers a wide range of health benefits. It is claimed that consuming passionflower concoction can help reduce the symptoms of diphtheria symptoms in just about a week. Just add a tablespoon of this powder to a cup of boiling water. Strain the concoction and drink it twice a day.

Castor leaves: Castor leaves contain anti-inflammatory and anti-microbial properties, which can help treat the condition effectively. Just take a few castor leaves and grind them. You can also add some drumstick

leaves and garlic juice to make a paste. Inhaling the aroma of this paste will clear your nasal passage and give you relief from the condition.

XI. Conclusion.

Symptoms of diphtheria begin with respiratory tract infection, with production of white-gray Pseudo-membrane. In severe cases can cause respiratory embarrassment and a bull-neck appearance. Complications include myocarditis, neurological toxicity, endocarditis and renal failure. Early diagnosis and treatment have better outcome. Seek immediate medical help if you think you or any member of your family has diphtheria. Just like any other disease, treatment is most effective when given early. Treatments for diphtheria include antibiotics and an antitoxin that neutralizes the infection. And here are some home remedies that can help treat this condition effectively. Harbal drugs such as Galic, Tulsi, Pinapple are used to contral the epidemic of Diphtheria. The treatment for diphtheria requires a compulsory hospital stay to prevent the spread of infection among family and friends. During this period, the patient is isolated from other patients to prevent the spread of infection to other immunized or non-immunized patients. Diphtheria infection can be prevented by spreading awareness about vaccinations

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