PRIMEVIEW

DIPHTHERIA

nature REVIEWS DISEASE PRIMERS

For the Primer, visit doi:10.1038/s41572-019-0131-y

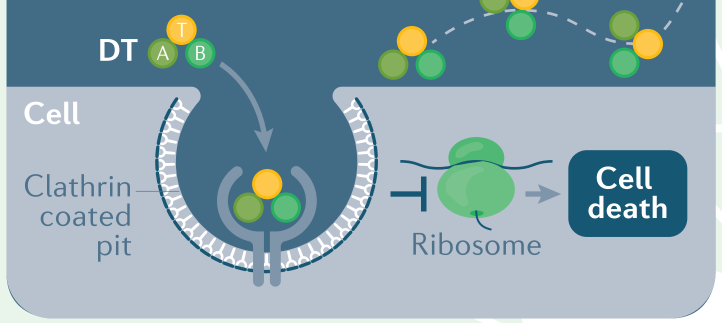
Diphtheria is a respiratory infection caused by toxigenic strains of *Corynebacterium diphtheriae* or, less frequently, *Corynebacterium ulcerans* or *Corynebacterium pseudotuberculosis*. Its pathological effects are due to diphtheria toxin (DT), which, in severe cases, can spread systemically and lead to myocarditis and polyneuropathy.

DIAGNOSIS

Clinical diagnosis is based on the typical signs of enlarged lymph nodes in the neck (bull neck) and the presence of a pseudomembrane (a thick layer of bacteria and cellular debris) in the throat. Microbiological confirmation is obtained by bacterial culture of swab samples, followed by identification of the causative species and toxigenicity tests; the Elek test (which is based on immunodiffusion — an antigen–antibody immunoprecipitation reaction) is the most commonly used test to assess the production of DT by the cultured bacterial colonies.

MECHANISMS

DT is an exotoxin secreted by *Corynebacterium* spp. that have acquired the DT-encoding gene (*tox*) from a bacteriophage (a virus). DT enters host cells by endocytosis; the catalytic subunit is then released into the cytosol, where it inhibits protein synthesis, leading to cell death.



EPIDEMIOLOGY

Diphtheria mostly affects children of <15 years of age

Case fatality rate is still 5-17% in non-vaccinated individuals

Non-toxigenic *C. diphtheriae* strains are a reservoir for the disease if they are infected by a tox-bearing bacteriophage, and are often associated with invasive infections

Global coverage with the DTP vaccine is >85%

Coverage rates in some countries are quite low, owing to socioeconomic factors that hamper healthcare systems and result in delayed or no vaccination

Molecular typing to identify similarities and differences between clinical isolates enables mapping of the geographical spread of the strains

MANAGEMENT

Diphtheria can be effectively treated with the timely administration of diphtheria antitoxin (DAT), which neutralizes circulating DT. Antibiotic therapy with oral penicillin V or erythromycin (or parenteral drugs if the throat infection prevents the patient from swallowing) for at least 2 weeks is recommended. Airway management and conventional cardiac treatment reduce mortality and, as polyneuropathy can have a late onset, patients should be followed up for 3–6 months.

PREVENTION

Effective vaccines are available. Three doses of a trivalent vaccine against diphtheria, tetanus and pertussis (DTP), to be given within the first 6 months of life, provide full protection. Close contacts of individuals with diphtheria should receive prophylactic treatment followed by immunization (the complete protocol or a booster dose, depending on the individual's immunization history).

OUTLOOK

Diphtheria is still a public health threat in countries where the vaccination programmes are not successfully implemented. Even in countries where the coverage is above the threshold for herd immunity, the disease could resurface, owing to the emergence of new toxigenic strains or declining immunization levels in adults. Thus, surveillance, both microbiological and epidemiological, is necessary for early detection of outbreaks. Prevention through vaccinations should be a priority, but improved DAT formulations are also required, as horse serum DAT might cause sensitization reactions, and its production is laborious.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps.

doi:10.1038/s41572-019-0139-3; Article citation ID: (2019) 5:82

Written by Lucia Brunello; designed by Laura Marshall