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BIOLOGICAL AGENTS

Tularaemia¹

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TULARAEMIAS CAUSED BY the intracellular pathogen *Francisella tularensis*, a small, pleomorphic, aerobic, Gram-negative coccobacillus which requires a complex cysteine-containing growth medium for laboratory cultures. Capsules may form in tissues.

The pathogen is not highly heat resistant but will survive freezing and drying. It survives well in the environment - especially in the cold with no direct sunlight and can remain viable in dried blood. *F. tularensis* is highly virulent - only a few organisms are required to cause illness in humans.

Two antigenically homologous isotypes exist, *Jellison* types A and B, which are differentiated epidemiologically, biochemically and by virulence. Two other subspecies also appear to have been isolated in the former Soviet Union and Japan, but these have not been characterised fully.

EPIDEMIOLOGY

F. tularensis is found throughout North America, Continental Europe, Japan, China and the former USSR, and can be isolated from a number of animal and insect vectors including rabbits, deer, deerflies, mosquitoes and ticks.

Jellison Type A (Nearctica) strain is present mainly in North America and is associated especially with wild rabbits, rodents, and blood-sucking arthropods. It is more virulent than Type B and can produce clinical symptoms from an inoculum with as few as 10 organisms untreated, this strain may cause death in 5 to 10 per cent of patients.

The ease of aerosolisation and the high virulence of Type A make it a serious biological hazard in laboratories.

Jellison Type B (Palearctic) strain is found in the Northern Hemisphere (Europe, Asia and America), particularly in water and aquatic animals. Infections often require inocula of more than 100,000 organisms, and fatalities in untreated cases are usually less than one per cent.

F. tularensis is most commonly transmitted to man by the bites of infected ticks or animals, inhalation of contaminated dust, ingestion of contaminated food or water, or direct contact with infected animal tissue. Man-to-man transmission is rare.

PATHOLOGY

Organisms which gain entry into the body may multiply at the site of entry, and spread to the regional lymph nodes, where they may disseminate via the bloodstream to other organs, especially the lungs,

liver and spleen. Organisms may persist intracellularly via the reticuloendothelial system, causing granulomatous lesions which may caseate or form small abscesses. Aggregates of *F. tularensis* may form in the spleen and the liver with a dense surrounding of polymorphonuclear cells (PMN's). These may progress to hepatic and splenic nodules with necrotic foci.

F. tularensis is primarily an intracellular parasite and survives in monocytes and other body cells. It may generate a persistent immune response and has a tendency to relapse. Cell-mediated immune responses are dominant, although opsonising antibodies (which appear later in the infection) are required for phagocytosis and intracellular killing of PMN's. Early tissue response may involve local necrosis, and the presence of neutrophils and macrophages.

CLINICAL MANIFESTATIONS

Clinical manifestations may be unapparent to fatal. The clinical symptoms are determined by the route of entry. Six different presentations may occur.

Ulceroglandular (Cutaneous)

The ulceroglandular type is the most common natural manifestation of the disease (75 to 85 per cent of cases) and usually results from direct contact with infected animals or tissues. The incubation period is usually three days.

A primary lesion develops at the site of inoculation, together with an abrupt onset of influenza-like symptoms (headache, fever, vomiting, generalised aching, diaphoresis, chills, myalgia, prostration). The organisms may spread to the regional lymph nodes, which become tender and enlarged.

After approximately one week, a popular lesion appears at the site of inoculation, which then ulcerates and breaks down with necrotic debris in the centre.

The patient usually remains febrile for two to three weeks, although fleeting muscular pain may last from two weeks to one month (and maybe intermittent for up to 12 months). Epistaxis and dizziness are common.

Glandular

The glandular form causes identical symptoms to ulceroglandular tularemia, but without the associated skin lesion.

Typhoidal (Enteric)

The typhoidal form occurs in approximately 10 per cent of cases. It may occur after the ingestion of contaminated food or water. The symptoms presented are very similar to those seen in typhoid fever, and may include fevers, chills, headache, anorexia and myalgia. No primary lesion is seen.

Necrotic ulcers form throughout the gastrointestinal tract, beginning with lesions and abscess formation around the mouth and pharynx. A severe sore throat, diarrhoea, abdominal pain, cough, shortness of breath, and ulcerative or exudative pharyngitis are characteristic. Gastrointestinal lesions may become haemorrhagic, and enlarged and tender lymph nodes may be seen. Toxaemia and death rapidly ensue if the patient is not treated promptly.

Oculoglandular (Conjunctival)

The oculoglandular form only occurs in 1 to 2 per cent of cases. Symptoms are very similar to ulceroglandular except that the primary lesion occurs around the eye.

The entire conjunctiva becomes inflamed and congested, followed by lacrimation, inflammation and enlargement of the pre-auricular lymphatic glands. A granular condition of the eyelids, chemosis (oedema of ocular conjunctiva resulting in swelling around the cornea), may be observed. Serious ocular damage may develop if the patient is not treated.

Pharyngeal

The pharyngeal form may occur as a result of typhoidal or ulceroglandular tularaemia. It appears as an exudative pharyngitis with associated lymphadenitis.

Pulmonary

The pulmonary form may be either primary (from inhalation of aerosol or contaminated dust) or as a secondary infection following bacteraemia and dissemination of the pathogen throughout the body or inhalation of bacteria from pharyngeal tularaemia.

Clinical symptoms include coughing, fevers, chills, headache, pleuritic chest pain, dyspnoea, non-productive cough and haemoptysis. Chest radiographs may reveal parenchymal infiltrates, pleuraleffusion and hilar lymphadenopathy. Conversely, there may be no enlarged lymph nodes, and the condition may resemble caseous tuberculous lesions. A systemic illness often follows.

Man-to-man spread through inhalation of respiratory droplets is possible. Pulmonary tularaemia is often fatal in up to 60 per cent of cases unless treated promptly¹.

All forms of tularaemia may result in systemic infection.

Although fatalities are uncommon, especially if the patient has been treated, a notable weakness and fatigue may remain for many months.

DIAGNOSIS Laboratory Diagnosis

Identification is generally made using clinical history, symptoms, and fluorescent antibody assays of smears from skin lesions, sputum or other specimens.

Positive identification can be made with isolation of the bacteria from blood or other tissues, although this can be hazardous (because of high infectivity of aerosols) and often unsuccessful due to the fastidious growth requirements of the organism.

Antibody detection is only useful as retrospective identification. Antibodies can be detected using agglutination or ELISA, although significant titres usually do not appear in the first week and may remain detectable for years. Therefore, diagnosis cannot be made on single titres. A fourfold increase in titres of acute and convalescent sera, taken at least one week apart, is a positive indication of infection.

Recently, a microagglutination test has been developed which can detect serum 1gM much earlier, and with a greater sensitivity than conventional agglutination methods.²

Diagnosis of infection following BW attack may be difficult because of the nonspecific symptoms presented, and a lack of suggestive exposure history.

Differential Diagnosis

Differential diagnoses are:

- Ulceroglandular: plague, toxoplasmosis, cat-scratch disease, chancroid, lymphogranuloma venereum.
- Pharyngeal: EBV infectious mononucleosis, streptococcal pharyngitis, diphtheria.
- Typhoidal: typhoid fever, brucellosis, leptospirosis, atypical pneumoniae.
- Pulmonary: Other pneumoniae, may resemble caseous tuberculous lesions.

TREATMENT

Streptomycin is the drug of choice, although some virulent resistant strains have been reported. Gentamycin³, erythromycin⁴ and tobramycin also seem effective. *F. tularensis* can be controlled by chloramphenicol and tetracyclines in aminoglycoside-sensitive patients, but relapses occur in more than one-third of the patients treated with these drugs.

Recommended therapy is as follows:

- Streptomycin 15-20 mg/kg/day intramuscularly for 10 to 14 days; or 30 to 40mg/kg/day in two divided doses for three days, followed by half that dose for the next four to seven days; or
- Gentamycin 3-5 mg/kg/day parenterally for 10 to 14 days.
- Post-exposure prophylaxis: tetracycline (2g/day orally) or doxycycline (200mg/day orally) for 14 days.

A favourable clinical response should be evident within 48 hours of therapy. Surgical drainage of fluctuant nodes should only be done after antibiotic therapy.

The patient requires bed rest for a prolonged period of time after pyrexia has subsided. A diet of high-calorie and easily digested foods is recommended. Convalescence is usually very slow and weakness may remain for many months.

Isolation is not usually necessary as human-to-human transmissions is unusual.

SUSCEPTIBILITY OF POPULATION

All ages are vulnerable and there is no difference in susceptibility between males and females.

PREVENTION

Solid immunity is usually acquired after a natural infection. Several different vaccines are available. These are currently only administered to at-risk personnel.

A live attenuated vaccine (LVS) derived from Strain 15 of the Palaeartic isotype and applied intradermally by multiple puncture has been used in the former USSR and to a limited extent in the USA. Side-effects appear minimal, usually only producing a mild local reaction with formation of a small papule. Approximately 25 per cent of patients acquire minimal axillary lymphadenitis, which spontaneously subsides. One in ten patients will experience a slight rise in body temperature. More than 95 per cent of vaccine recipients will exhibit antibody and cell-mediated immune responses. LVS has been shown to prevent laboratory-acquired infections and experimental airborne disease. Protection can be overcome with large infective doses.

An aerogenic tularaemia vaccine (developed at Fort Detrick, Maryland), and administered by inhalation appears to be more effective than injected vaccines.

Killed vaccines do not appear to be very successful. A multiple BW agent vaccine is currently being developed in Canada.

Passive immune therapies for humans are probably not feasible because protection seems more cell-mediated than humoral.

POTENTIAL AS BW

The most significant consequences of an attack of tularaemia are the debilitating effects rather than the mortality. The length of initial illness and long convalescence would strain medical resources and seriously deplete effective manpower.

The infectious dose in air is very low (10 to 50 organisms). *F. tularensis* has a high persistence in the environment, on dry surfaces and in the wet.

A BW attack would most likely involve aerosols and cause pulmonary tularaemia, which could result in high morbidity and possible mortality of 5 to 10 per cent. Symptoms are often nonspecific, and diagnosis may be difficult.

FUTURE DIRECTIONS

Recent research has indicated that several other antibiotics may be useful in treating tularaemia. Orally administered fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin and perfloxacin) show some potential⁶; imipenem/cilastin sodium (Primaxin) may also be effective⁷. The efficacies of these drugs are being further studied.

Recombinant vaccines are currently being investigated. Recombinant techniques expressing the 17 kDa membrane lipoprotein have been shown to elicit a T-cell response in humans⁹ although a combination of several proteins may be necessary for optimal protection.

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