

Brucellosis

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دانشجو در پایان جلسه بیماری بروسلوز باید بتواند:

- ۱- روش های انتقال بیماری بروسلوز را برشمارد
- ۲- مشخصات باکتریولوژیک میکروب بروسلا را بیان کند
- ۳- علایم بالینی بیماری را برشمارد
- ۴- نکات برجسته در معاینه فیزیکی را بیان کند
- ۵- روشهای تشخیصی بیماری بروسلوز را برشمارد
- ۶- موارد مثبت کاذب و منفی کاذب تستهای سرولوژیک بروسلوز را بیان کند
- ۷- تستهای سرولوژی مربوطه را در یک بیمار تفسیر نماید

- Human brucellosis is caused by organisms of the genus Brucella and continues to be a major public health problem worldwide
- Humans are accidental hosts and acquire this zoonosis from direct contact with an infected animal (cattle, sheep, camels, goats, and pigs)/ consumption of products of an infected animal
- Although brucellosis is widely recognized as an occupational risk among adults working with livestock, much of the brucellosis in children is **food-borne** and is associated **with consumption of unpasteurized dairy products**
- Brucella spp. are also potential agents of bioterrorism

Etiology

- ✓ *Brucella abortus* (cattle), *Brucella melitensis* (goats and sheep), *Brucella suis* (swine), and *Brucella canis* (dogs) are the most common organisms responsible for human disease
- ✓ These organisms are small, aerobic, non-spore forming, nonmotile, **gram-negative coccobacillary bacteria**
- ✓ *Brucella* spp. fastidious in their growth but can be grown on various laboratory media, including blood and chocolate agars

Epidemiology

- Brucellosis is endemic in many parts of the world and is especially prevalent in the Mediterranean basin, Persian Gulf, Indian subcontinent, and parts of Mexico and Central and South America
- There are approximately 500,000 new cases annually worldwide, although accurate estimates of the prevalence of disease are lacking because of underreporting and underdiagnosis

*Epidemiology**

- Childhood brucellosis, 10–30% of cases
- *B. melitensis* is the most prevalent species causing human brucellosis and is most often carried by sheep, goats, camels, and buffalo
- A history of **travel to endemic regions/ consumption of exotic food/unpasteurized dairy products** may be an important clue to the diagnosis of human brucellosis
- **All age-groups** can be infected by *Brucella*, and infections are more common **in males**, likely because of more frequent occupational and environmental exposures

Pathogenesis

Modes of transmission for these organisms:

- Inoculation through cuts/abrasions in the skin
- Inoculation of the conjunctiva
- Inhalation of infectious aerosols
- Ingestion of contaminated meat/dairy products
- In children the primary means of infection is through eating /drinking unpasteurized/raw dairy products
- Individuals in endemic areas with occupational exposures to animals(farmers and veterinarians)

*Pathogenesis**

- ❑ Laboratory workers are more often exposed to infected aerosols
- ❑ The risk for infection depends on the nutritional and immune status of the host, the route of inoculum, and the species of Brucella
- ❑ *B. melitensis* and *B. suis* are more virulent than *B. abortus*/*B. canis*
- ❑ The major virulence factor for Brucella, its cell wall lipopolysaccharide

- ❑ Strains containing smooth LPS have been demonstrated to have greater virulence and are more resistant to killing by polymorphonuclear leukocytes

- ❑ These organisms are facultative intracellular pathogens that can survive and replicate within the mononuclear phagocytic cells (monocytes, macrophages) of the reticuloendothelial system

Brucella spp

- The leukocytes are less efficient at killing these organisms than other bacteria despite the assistance of serum factors such as complement
- Possess multiple strategies to evade immune responses and establish and maintain chronic infection. Specifically, during chronic stages of infection
- Persist within the liver, spleen, lymph nodes, and bone marrow and result in granuloma formation

*Brucella spp**

- **Antibodies** are produced against the LPS and other cell wall antigens, providing a means of diagnosis and probably playing a role in long-term immunity
- The major factor in recovery from infection appears to be development of a **cell-mediated response**, resulting in macrophage activation and enhanced intracellular killing
- Specifically, sensitized T lymphocyte release cytokines (interferon- γ , tumor necrosis factor- α), which activate the macrophages and enhance their intracellular killing capacity

Clinical Manifestations

- ❖ A systemic illness that can be very difficult to diagnose in children. Symptoms can be acute /insidious in nature and are usually nonspecific
- ❖ The incubation period, 2-4 wk but may be shorter with *B. melitensis*
- ❖ Fever, in >95% of cases, the fever pattern can vary widely

- ❖ The most common physical complaints, arthralgia, myalgia, and back pain
- ❖ Systemic symptoms, fatigue, sweats, chills, anorexia, headache, weight loss, and malaise, in the majority of adult cases, less frequent in children

- ❖ Abdominal pain, diarrhea, rash, vomiting, cough, and pharyngitis

Physical Manifestation

- Hepatic and splenic enlargement, (50%)
- Arthralgia is common, arthritis, in a minority of cases
- Arthritis, monoarticular, involves the knee/hip in children and the sacroiliac joint (in adolescents and adults)
- No typical rash for this infection
- Epididymo-orchitis more common in adolescents and adults
- Because of the organism's ability to establish chronic infection, hepatic and splenic abscesses may develop

Serious Manifestations

- Endocarditis, meningitis, osteomyelitis, and spondylitis
- Although headache, mental inattention, and depression may be demonstrated in patients with uncomplicated brucellosis, invasion of the nervous system (1–4%)
- Neonatal and congenital infections resulting from transplacental transmission, breast milk, and blood transfusions
- The signs and symptoms associated with congenital/neonatal brucellosis, nonspecific
- Hematologic abnormalities are common, thrombocytopenia, leukopenia, anemia, pancytopenia
- Hemolytic complications, microangiopathic hemolytic anemia, autoimmune hemolytic anemia
- Elevations of liver enzymes (50%)

Diagnosis

- A definitive diagnosis of brucellosis, by recovering the organisms from the blood, bone marrow, other tissues
- Unfortunately, cultures are insensitive and positive only in a minority of cases
- Isolation of the organism may require as long as 4 wk from a blood culture sample unless the laboratory is using an automated culture system such as the lysis-centrifugation method, where the organism can be recovered in 5-7 days
- It is prudent to alert the clinical microbiology laboratory that brucellosis is suspected so that cultures can be held longer
- Bone marrow cultures may be superior to blood cultures when evaluating patients who have received previous antimicrobial therapy
- Because of the low yield of cultures, various serologic tests have been applied to the diagnosis of brucellosis

*Diagnosis**

- The serum agglutination test (Wright test) is the most widely used and detects antibodies against *B. abortus*, *B. melitensis*, and *B. suis*
- This method does not detect antibodies against *B. canis* because this species lacks the smooth LPS; *B. canis* specific antigen is required
- No single titer is ever diagnostic, but most patients with acute infections have titers of ≥ 160 . Antibodies can generally be detected within 2-4 wk after infection
- Low titers may be found early in the course of the illness, requiring the use of acute and convalescent era testing to confirm the diagnosis: 4-fold increase titers drawn ≥ 2 wk apart

*Diagnosis***

- Because patients with active infection have both an immunoglobulin M (IgM) and an IgG response and the serum agglutination test measures the total quantity of agglutinating antibodies, the total quantity of IgG measured by treatment of the serum with γ -mercaptoethanol
- This fractionation is important in determining the significance of the antibody titer, because low levels of IgM can remain in the serum for weeks to months after the infection has been treated
- IgG titers decrease with effective therapy, and a negative γ -mercaptoethanol test after treatment indicates a favorable response

*Diagnosis****

- It is important to remember that all serologic results must be interpreted in light of a patient's history and physical examination
- False-positive results from cross-reacting antibodies to other gram-negative organisms, *Yersinia enterocolitica*, *Francisella tularensis*, and *Vibrio cholerae*, can occur
- In addition, the prozone effect can give false-negative results in the presence of high titers of antibody
- To avoid this issue, serum that is being tested should be diluted to $\geq 1:320$.

CONT''

- The enzyme immunoassay should only be used for suspected cases with negative serum agglutination tests/ for the evaluation of patients in the following situations:(¹) complicated cases, (²) suspected chronic brucellosis, (³) reinfection
- Polymerase chain reaction(PCR) assays have been developed but are not available in most clinical laboratories

Differential Diagnosis

- ❖ Fever of unknown origin(FUO) in endemic areas
- ❖ Tularemia, cat-scratch disease, malaria, typhoid fever, histoplasmosis, blastomycosis, and coccidioidomycosis
- ❖ Infections caused by *Mycobacterium tuberculosis*, atypical mycobacteria, rickettsiae, and *Yersinia* can also present similar to brucellosis



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