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The Crux

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CONTENTS

Editorial

Brucellosis is a zoonosis caused by ingestion of unpasteurized milk from infected animals, or close contact with their secretions. It is also known as **undulant fever**, **Malta fever**, and **Mediterranean fever**.

The bacteria causing this disease, *Brucella*, are small, Gram-negative, nonmotile, nonspore-forming, rod-shaped (coccobacilli) bacteria. They function as facultative intracellular parasites, causing chronic disease, which usually persists for life. Four species infect humans: *B. abortus*, *B. canis*, *B. melitensis*, and *B. suis*. *B. abortus* is less virulent than *B. melitensis* and is primarily a disease of cattle. *B. canis* affects dogs. *B. melitensis* is the most virulent and invasive species; it usually infects goats and occasionally sheep. *B. suis* is of intermediate virulence and chiefly infects pigs. Symptoms include profuse sweating and joint and muscle pain. Brucellosis has been recognized in animals and humans since the early 20th century.

In the first stage of the disease, bacteremia occurs and leads to the classic triad of undulant fevers, sweating (often with a characteristic foul, moldy smell sometimes likened to wet hay), and migratory arthralgia and myalgia (joint and muscle pain). Blood tests characteristically reveal a low number of white blood cells and red blood cells, show some elevation of liver enzymes such as aspartate aminotransferase and alanine aminotransferase, and demonstrate positive Bengal rose and Huddleston reactions. Gastrointestinal symptoms occur in 70% of cases and include nausea, vomiting, decreased appetite, unintentional weight loss, abdominal pain, constipation, diarrhea, an enlarged liver, liver inflammation, liver abscess, and an enlarged spleen.

The symptoms are like those associated with many other febrile diseases, but with emphasis on muscular pain and night sweats. The duration of the disease can vary from a few weeks to many months or even years. All in all it is a tricky fever to diagnose clinically and usually goes undiagnosed initially. **"DISEASE DIAGNOSIS"** clarifies all your doubts regarding this often missed disease known as **"BRUCELLOSIS"**

When the main topic is a fever, the other important components of the communiqué have been aimed at PUOs or FUOs. **INTERPRETATION** and **TROUBLE SHOOTING**, both talk about Pyrexias of Unknown Origins.

We take immense pride in introducing **"PYROCHECK"** that diagnoses three common fevers in one go.

Enjoy the non technical pages too!

DISEASE DIAGNOSIS

BRUCELLOSIS

Cattle, goats, sheep, dogs, pigs

Background

Brucellosis is a zoonotic infection caused by the bacterial genus *Brucella.* The bacteria are transmitted from animals to humans by ingestion through infected food products, direct contact with an infected animal, or inhalation of aerosols. The disease is an old one that has been known by various names, including Mediterranean fever, Malta fever, gastric remittent fever, and undulant fever. Humans are accidental hosts, but brucellosis continues to be a major public health concern worldwide and is the most common zoonotic infection. *Brucella* organisms, which are small aerobic intracellular coccobacilli, localize in the reproductive organs of host animals, causing abortions and sterility. They are shed in large numbers in the animal's urine, milk, placental fluid, and other fluids. Twelve species have been identified, named primarily for the source animal or features of infection. Of these, the following 4 have moderate-to-significant human pathogenicity:

- *Brucella melitensis (from sheep; highest pathogenicity)*
- *Brucella suis* (from pigs; high pathogenicity)
- *Brucella abortus* (from cattle; moderate pathogenicity)
- *Brucella canis* (from dogs; moderate pathogenicity)

Although domesticated animals are of particular importance, brucellosis is also found in wild animals that exist in herds (eg, bison or elk in North America and wild boar in Germany). Humans have only a limited risk from wild animals, mainly because of lack of proximity or intimate contact and infrequent use of milk and meat products from these animals. Concerns have been voiced that interaction of wild animals with domesticated ones may lead to infection of agricultural herds, though supportive evidence is quite limited. The global burden of human brucellosis remains enormous. The organism causes more than 500,000 infections per year worldwide. The annual number of reported cases in United States (about 100) has dropped significantly because of aggressive animal vaccination programs and milk pasteurization. Most US cases are now due to the consumption of imported unpasteurized dairy products from Mexico. Approximately 60% of human brucellosis cases in the United States now occur in California, Texas, Arizona, and Florida. Interest in brucellosis has been increasing because of the growing phenomena of international tourism and migration, in addition to the potential use of *Brucella* as a biological weapon. Familiarity with the manifestations of brucellosis and knowledge of the optimal laboratory studies are essential for the recognition of this reemerging zoonosis. *B melitensis, B abortus,* and *B suis* have been completely sequenced, and these sequencing data will help improve our understanding of the pathogenesis and the manifestations of this complex disease. Definitive diagnosis of brucellosis is based on culture, serologic techniques, or both. Clinically, identification to the genus level is sufficient to warrant initiation of therapy. The particular *Brucella* species involved does not affect the choice of therapeutic agents; however, speciation is necessary for epidemiologic surveillance and requires more detailed biochemical, metabolic, and immunologic testing.

Pathophysiology

Brucellae are aerobic gram-negative coccobacilli that possess a unique ability to invade both phagocytic and nonphagocytic cells and to survive in the intracellular environment by finding ways to avoid the immune system. This ability helps explain why brucellosis is a systemic disease and can involve almost every organ system. *Brucella* can gain entry into the human body through breaks in the skin, mucous membranes, conjunctivae, and respiratory and gastrointestinal (GI) tracts. Sexual transmission has not been convincingly documented. Ingestion usually occurs by way of unpasteurized milk; meat products often have a low bacterial load. In the United States, percutaneous needlestick exposure, conjunctival exposure through eye splash, and inhalation are the most common routes of entry. Once within the bloodstream, the organisms quickly become intracellular pathogens contained within circulating polymorphonuclear cells (PMNs) and macrophages, making use of numerous mechanisms to avoid or suppress bactericidal responses. Animal data suggest that the lipopolysaccharide (LPS) coat (smooth in *B melitensis, B abortus,* and *B suis;* rough in *B canis*) is likely to play a role in intracellular survival, perhaps because of adenine and guanine monophosphate production, which inhibits phagosomal fusion and oxidative burst activity. In addition, *Brucella* species have relatively low virulence, toxicity, and pyrogenicity, making them poor inducers of some inflammatory cytokines, such as tumor necrosis factor (TNF) and interferons. Furthermore, the bacteria do not activate the alternative complement system. Finally, they are thought to inhibit programmed cell death. After ingestion by phagocytes, about 15-30% of brucellae survive. Susceptibility to intracellular killing differs among species, with *B abortus* readily killed and *B melitensis* rarely affected; these differences might explain the differences in pathogenicity and clinical manifestations in human cases of brucellosis. Brucellae that survive are transported into the lymphatic system and may replicate there locally; they also may replicate in the kidney, liver, spleen, breast tissue, or joints, causing both localized and systemic infection. Any organ system can be involved (eg, central nervous system [CNS], heart, joints, genitourinary system, pulmonary system, and skin); localization of the process may cause focal symptoms or findings. After replication in the endoplasmic reticulum, the brucellae are released with the help of hemolysins and induced cell necrosis. Development of cell-mediated immunity is the principal mechanism of recovery. The host response to infection with *B abortus* is characterized by the development of tissue granulomas indistinguishable from those of sarcoidosis. In contrast, infection with the more virulent species (*B melitensis* and *B suis*) more commonly results in visceral microabscesses. Although *Brucella* infection is primarily controlled through cell-mediated immunity rather than antibody activity, some immunity to reinfection is provided by serum immunoglobulin (Ig). Initially, IgM levels rise, followed by IgG titers. IgM may remain in the serum in low levels for several months, whereas IgG eventually declines. Persistently elevated IgG titers or second rises in IgG usually indicate chronic or relapsed infection. IgA antibodies are elaborated late and also may persist for very long intervals.

Etiology

Brucellosis is caused by infection with *Brucella* species. The traditional classification of these species is based primarily on the preferred hosts.

Table 1. Currently Recognized *Brucella* Species

Organism	Animal Reservoir	Geographic Distribution
Brucella melitensis	Goats, sheep, camels	Mediterranean, Asia, Latin America, parts of Africa and some southern European countries
Brucella abortus	Cows, buffalo, camels, yaks	Worldwide
Brucella suis	Pigs (biotype 1-3)	South America, Southeast Asia, United States
Brucella canis	Canines	Cosmopolitan
Brucella ovis	Sheep	No known human cases
Brucella neotomae	Rodents	Not known to cause human disease
Brucella pinnipediae and *Brucella cetaceae*	Marine animals, minke whales, dolphins, seals	Case reports describing some human cases (mainly neurobrucellosis)
Brucella inopinata	unknown	Case report of human infection of a breast implant
Brucella microti	Voles	South Moravia, Czech Republic
Brucella papionis	Baboons	Tanzania
Brucella vulpis	Foxes	Austria

Of the 4 *Brucella* species known to cause disease in humans (*B abortus, B melitensis, B canis, B suis*), *B melitensis* is thought to be the most virulent and causes the most severe and acute cases of brucellosis; it is also the most prevalent worldwide. *B melitensis* may be acquired via exposure to animals or animal products or, in the case of laboratory technicians, to specimens from animals (including humans) whose tissues are operated upon or submitted for culture or pathologic analysis. *B abortus* is more widely distributed throughout the world than *B melitensis* is, but it is less pathogenic for both animals and humans. It has, however, been the most common cause of brucellosis in North America. This species gives rise to mild-to-moderate sporadic disease that rarely causes complications. *B suis* has been the second most common cause of brucellosis in North America. Infection with this species gives rise to a prolonged course of illness, often associated with suppurative destructive lesions. *B canis* infection has a disease course that is indistinguishable from that of *B abortus* infection. It infection has an insidious onset, causes frequent relapses, and does not commonly cause chronic brucellosis. Although *B pinnipediae* and *B cetaceae* typically affect marine animals, they are now known to be capable of causing disease in humans (mainly neurobrucellosis). Ingestion of unpasteurized goat milk and related dairy products is the main route by which *B melitensis* is transmitted to humans. Slaughterhouse workers, primarily those in the kill areas, become inoculated with brucellae through aerosolization of fluids, contamination of skin abrasions, and splashing of mucous membranes. Farmers and shepherds have similar exposure risks, and they also have exposure to aborted animals. Veterinarians are usually infected by inadvertent inoculation of animal vaccines against *B abortus* and *B melitensis*. Laboratory workers (microbiologists) are exposed by processing specimens (aerosols) without special precautions. Occupational exposures tend to be isolated. A large-scale outbreak of the infection should raise suspicion that a biologic weapon has been released, most likely via an infectious aerosol.

Epidemiology

International statistics

Brucellosis causes more than 500,000 infections per year worldwide. Its geographic distribution is limited by effective public and animal health programs, and the prevalence of the disease varies widely from country to country. Overall, the frequency of brucellosis is higher in more agrarian societies and in places where handling of animal products and dairy products is less stringent. European Union (EU) data suggest that there is a clear (though nonlinear) association between gross domestic product (GDP) and rates of brucellosis. According to these data, no countries with a GDP above 90% of the mean had an annual incidence of brucellosis higher than 10 cases per million population. The heaviest disease burden lies in countries of the Mediterranean basin and Arabian Peninsula, and the disease is also common in India, Mexico, and South and Central America. Although some countries (eg, the United Kingdom and Ireland) have effectively controlled brucellosis, new areas of human brucellosis have emerged in areas such as central and southwest Asia. Because of variable reporting, true estimates in endemic areas are unknown. Incidence rates of 1.2-70 cases per 100,000 people are reported. In very resource-poor countries (such as some African countries) in which brucellosis is endemic, control through animal slaughter is a poor option because of the fragile nature of the food supply. Brucellosis was recently reported in a tick species in the Inner Mongolia region of China. In a systematic review commissioned by the World Health Organization (WHO) with the goal of determining a disability weight for clinical manifestations of human brucellosis, the investigators proposed a disability weight of 0.150 for chronic localized brucellosis and 0.190 for acute brucellosis. These estimates were based on disability weights from the 2004 Global Burden of Disease Study. Further study is required before a consensus can be reached.

Age-related demographics

Brucellosis in the Mediterranean, chiefly due to *B melitensis*, has the highest age/sex-related incidence in males in their mid-20s. A report

from northern Saudi Arabia found that 60% of cases of brucellosis occurred in individuals aged 13-40 years, whereas 21% occurred in those younger than 13 years, 16% in those aged 40-60 years, and 2.5% in those older than 60 years. For unknown reasons, men aged 13-40 years are particularly vulnerable to the manifestation of illness due to *B melitensis*. Possible explanations include engaging in activities that increase exposure to *Brucella* organisms (eg, animal husbandry) and less diligent personal hygiene. The predilection is not universal, given that 60% of cases in Jordan occur in individuals younger than 24 years. Elderly individuals with acute localized brucellosis are particularly likely to manifest destructive localized brucellosis of the spine. Brucellosis is generally uncommon in infants. The international literature suggests that brucellosis may be more common in children in developing countries because of lack of pasteurization and working in an agrarian society. Transmission to infants may occur through breastfeeding or ingestion of raw milk. Prepubertal children account for less than 2% of all cases of neurobrucellosis; fewer than 50 such cases have been described in the peer-reviewed medical literature over the past 50 years.

Sex-related demographics

Worldwide, brucellosis is more common in males than in females. Young adult males predominate in most series of patients with brucellosis compiled in areas of endemic disease. A report from northern Saudi Arabia found a male-to-female ratio of 1.7:1, chiefly individuals aged 13-40 years. The cases represented in such series are caused chiefly by *B melitensis*. Occupational exposure to animals likely plays an important role in the enhanced vulnerability of men to the development of brucellosis. Whether the increased risk manifested by males is additionally influenced by aspects of personal hygiene, immunologic factors, or other circumstances is not known. Food-borne brucellosis is not limited according to age or sex and is found in women and men in equal numbers.

Race-related demographics

Exposures tend to be primarily occupational; accordingly, no racial predilection has been identified in the United States.

Prognosis

The prognosis is generally excellent. Although initial symptoms of brucellosis may be debilitating, if they are treated appropriately and within the first few months of onset, the disease is easily curable, with a low risk of relapse or chronic disease. However, the prognosis is poor in persons who present with congestive heart failure due to endocarditis, in whom mortality approaches 85%. In some patients, brucellosis can cause chronic debilitating illness with extensive morbidity. In uncomplicated cases of acute brucellosis, fever, malaise, and many other manifestations improve rapidly with bed rest, whereas sustained physical activity may prolong or worsen the degree of illness. Considerable improvement from the symptoms of the acute phase of illness typically occurs within a few weeks, with or without treatment. In many cases, this is followed by complete remission within 2-6 months. Recovery tends to be more rapid with *B abortus* infection than with *B melitensis* or *B suis* infection. Overall mortality in recognizably symptomatic acute or chronic cases of brucellosis is very low, certainly less than 5% and probably less than 2%. It is usually the result of the rare instance of *Brucella* endocarditis or is the result of severe CNS involvement, often as a complication of endocarditis. Postmortem analysis confirms that the burden of acute brucellotic infection is borne by tissues of the lymphoreticular system. Recurrence of symptoms of acute brucellosis is not uncommon. The recurrent disease may be systemic or localized. In some of these patients, the condition evolves into chronic brucellosis, which may be progressive if untreated. Chronic brucellosis includes systemic and specific localized forms (including various types of neurobrucellosis). These various forms are due to continued infectious disease, for which additional treatment is indicated and effective. Objective clinical and laboratory evidence for ongoing disease is demonstrable. Patients who do not have such evidence and who complain of occasional mild symptoms similar to those found in acute brucellosis are likely to have psychoneurosis. This complication of acute brucellosis does not usually resolve with anti-brucellosis treatments, although such treatments may exert placebo effects for individual bouts. Psychiatric treatment may be indicated. The likelihood of recurrence is greater in individuals who are not treated or who are inadequately treated for acute brucellosis. However, recurrence is possible even in properly treated patients who have had acute brucellosis. Addition of oral rifampicin to oral tetracycline may reduce the recurrence risk for patients who are treated with that combined therapy for acute brucellosis. Chronic brucellosis may continue to trouble patients for as long as 25 years, but such cases are quite rare.

Patient Education

Patient education should include efforts to address the following issues:

- The nature of the disease and the routes by which it can be transmitted
- The symptoms, complications, and treatment of the disease, as well as the risk of relapse if it is not adequately treated
- The potential adverse effects of the medications administered
- The need for strict compliance with the antibiotic regimen
- In soma case, reassurance concerning recurrent symptoms that are not associated with clinical or laboratory evidence of acute brucellotic disease
- The need to avoid potential sources of infection – This may involve avoiding infected animals, using stricter precautions (eg, gloves and mask) when dealing with a potentially infected animal, or avoiding potentially contaminated foods
- For farmers and ranchers, immunization of their cattle against the disease as necessary
- For laboratory workers, maintenance of the appropriate level of containment.

Clinical Presentation

History

A careful history is the most helpful tool in the diagnosis of brucellosis. The history should include both assessment of any risk factors present and evaluation of any symptoms reported. Unless exposure to *Brucella* is due to a weaponized attack, almost every case of brucellosis involves exposure to an affected animal in some fashion, either directly or indirectly.

Risk factors

The risk factors for brucellosis differ somewhat, depending upon whether a given individual resides in or has recently visited a region of endemic disease.

Endemic exposure

Brucellosis should be considered in any patient whose place of residence or dietary, travel, or occupational history suggests a risk for the infection and who is experiencing any of the various known neurologic or nonneurologic complications of brucellosis. It must be borne in mind that the latency period from infection to onset of symptoms of primary brucellosis may be as long as months. The threshold for consideration of brucellosis is low in regions of endemic disease, where diagnostic

testing is undertaken for any of the many atypical presentations or unusual complications. A dietary history is especially helpful for diagnosing brucellosis in individuals who live in or visit regions of endemic disease. Unpasteurized dairy products, especially goat's cheese, frequently are implicated as sources of human infection. Raw or poorly cooked meats are also important sources of infection in regions of endemic disease. Occasional person-to-person transmission has been reported, including transmission to infants via breastfeeding. There is a little evidence for sexual transmission of brucellosis. Laboratory transmission of brucellosis may occur, especially in regions of endemic disease. It is estimated that 12% of laboratory workers in Spain acquire brucellosis.

Nonendemic exposure

Brucellosis poses a particular diagnostic challenge in persons not from regions of endemic disease. In areas of the world where brucellosis is rare, the diagnosis may be missed even in patients who manifest typical signs, such as otherwise uncomplicated persistent undulating fever. The possibility of brucellosis is even less likely to be recognized promptly in cases that present atypically. A dietary history is important in evaluating for the possibility of brucellosis among individuals who live in regions where the disease is not endemic because the disease may be acquired through ingestion of infected foods shipped from regions of endemic disease. Ingestion of unpasteurized milk from cows or goats enhances risk of infection in both regions of endemic disease and regions in which the disease is not endemic. Although various potential intermediate hosts have harbored brucellosis in the extra-Mediterranean world, dairy cattle infected with *B abortus* have been particularly important hosts in North America. The infection is often symptomatic in cattle. Outbreaks of epizootic bovine abortion due to *B abortus* should alert health care providers to the possibility of human brucellosis. Some cases in humans in North America have been traced to pork from hogs infected with *B suis*. In Scandinavia and Alaska, reindeer are an important source of brucellosis. Brucellosis has developed in infants who have been breastfed from mothers who either visited regions of endemic disease or ingested foodstuffs shipped from such regions. In nonendemic regions, as in endemic regions, physicians, veterinarians, pathologists, and laboratory personal exposed to tissues from infected animals (including humans) are at particular risk for brucellosis. Surprisingly, infection with *Brucella* species accounts for as many as 10% of laboratory-acquired infections, 24% of laboratory-acquired bacterial infections, and 11% of occupational-exposure deaths in the United States. Aside from laboratory workers, individuals at greatest risk for brucellosis are those exposed to goats, sheep, cows, camels, pigs, reindeer, rabbits, or hares, both in areas of endemic disease and in areas where the disease is not endemic. Such individuals include herders, hunters, farmers, dairy workers, veterinarians, abattoir workers, and meatpackers. *Brucella* has the potential to be used as a biologic weapon, but to date, these organisms have not been implicated in any major bioterrorism incident. Were they used in such a way, however, patients might not present until several weeks later. Because of this potential, and in view of the rarity of brucellosis in the United States, especially in more urban areas, any clustering of brucellosis cases should be thoroughly investigated and reported to public health officials.

Symptoms

Symptoms of brucellosis are protean in nature, and none is specific enough to support the diagnosis. Fever is the most common symptom and sign of brucellosis, occurring in 80-100% of cases. It is intermittent in 60% of patients with acute and chronic brucellosis and undulant in 60% of patients with subacute brucellosis. Fever can be associated with a relative bradycardia. Fever of unknown origin (FUO) is a common initial diagnosis in patients in areas of low endemicity. It is associated with chills in almost 80% of cases. Constitutional symptoms of brucellosis include anorexia, asthenia, fatigue, weakness, and malaise, and weight loss and are very common (> 90% of cases). Bone and joint symptoms include arthralgias, low back pain, spine and joint pain, and, rarely, joint swelling. These symptoms affect as many as 55-80% of patients. Arthralgias may be diffuse or localized, with a predilection for bone ends and the sacroiliac joint. Acute monoarticular arthritis is uncommon but may be part of the presentation. Neuropsychiatric symptoms of brucellosis are common despite the rare involvement of the nervous system. Headache, depression, and fatigue are the most frequently reported neuropsychiatric symptoms. In patients with advanced disease who have meningoencephalitis, these complaints may include changes in mental status, coma, neurologic deficit, nuchal rigidity, or seizures. A significant percentage (approximately 50%) of patients have gastrointestinal (GI) complaints, primarily dyspepsia, though abdominal pain from hepatic abscesses may occur. Hepatic abscesses should be suspected in patients with signs of systemic toxicity and persistently elevated liver enzymes. The abscess can serve as a source of bacteremic seeding. Spontaneous bacterial peritonitis secondary to brucellosis infection has been reported. Constipation, diarrhea, and vomiting may occur. Genitourinary infections with brucellae have been reported and include orchitis, urinary tract infection (UTI), and glomerulonephritis. Frank renal failure or sepsis is rare. Neurologic symptoms of brucellosis can include weakness, dizziness, unsteadiness of gait, and urinary retention. Symptoms associated with cranial nerve dysfunction may affect persons with chronic central nervous system (CNS) involvement. Cough and dyspnea develop in up to 19% of persons with brucellosis; however, these symptoms are rarely associated with active pulmonary involvement. Pleuritic chest pain may affect patients with underlying empyema. Endocarditis from brucellae is reported, with septic embolization a common complication of this form of brucellosis. Other cardiac complications, such as pulmonary edema or dysrhythmias, are rare. *Brucella* endocarditis is the form most commonly associated with fatalities. With the chronic form of brucellosis, in which the illness has lasted longer than 1 year (undiagnosed and untreated brucellosis), an afebrile pattern is typical, with a history of myalgia, fatigue, depression, and arthralgias (chronic fatigue syndrome is the most important disease in the differential diagnosis). The chronic form is primarily caused by *B melitensis* and usually affects adults older than 30 years. The chronic form is rare in children.

Physical Examination

Generally, physical examination findings are normal or only minimally abnormal (see below), and the diagnosis is made on the basis of the history and serologic studies.

Categorization of disease

Traditionally, brucellosis has been classified as subclinical, acute, subacute, or chronic; localized and relapsing forms have also been described. This classification system, though commonly used, is subjective and of limited clinical utility.

Subclinical brucellosis

Disease is usually asymptomatic, and the diagnosis is usually established incidentally after serologic screening of persons at high risk of exposure. Culture data are usually unrevealing.

Acute and subacute brucellosis

Disease can be mild and self-limited (eg, *B abortus*) or fulminant with severe complications (eg, *B melitensis*). Associated symptoms can

develop 2-3 months before diagnosis in mild cases and 3-12 months before diagnosis in severe cases. Usually, acute brucellosis occurs without focal abnormalities. Non focal weakness may be noted. The tissues overlying the spine or peripheral nerves may be tender to percussion. Tenderness, swelling, or effusion of joints may be evident. In some instances, orchitis appears after a few days of illness. Testicular swelling and tenderness in the wake of chills and high fever thus resemble mumps orchitis. Some patients manifest constipation. Occasionally, abdominal tenderness suggests an acute abdomen. In some more severe cases, tender enlargement of the spleen may be detected. Murmurs, friction rubs, acute-onset blindness or visual field disturbance, tachycardia, oropharyngeal or conjunctival petechiae (some with pale centers), Roth spots, splinter hemorrhages of the nail beds, Osler nodes, Janeway lesions, or hepatosplenomegaly may develop as manifestations of bacterial endocarditis, a complication that is much rarer as an aspect of acute or subacute brucellosis than as an element of focal or diffuse chronic brucellosis. Rarely, disease of the lungs or pleura is a feature of acute brucellosis, manifestations of which could include rales, wheezes, abnormalities of percussion or egophony, or pleural friction rubs. Meningismus, papilledema, mental status changes, and long-tract signs are found in a small fraction of cases of acute brucellosis as manifestations of acute neurobrucellosis. Radicular sensory or motor changes may arise in individuals with brucellotic osteomyelitis with associated epidural abscess. Focal tenderness or pain in the perispinous region may precede fever and objective sensory or motor findings. Brucellotic cervical epidural abscess may produce tenderness and movement restriction without the classic triad (fever, neck pain, and radiculopathy) of streptococcal or other types of epidural abscess. However, such findings may eventually develop, prompting delayed consideration of this diagnostic entity.

Chronic brucellosis

The diagnosis of chronic brucellosis is typically made after symptoms have persisted for 1 year or more. Low-grade fevers and neuropsychiatric symptoms predominate. Results of serologic studies and cultures are often negative; without confirmatory evidence, many authorities doubt the existence of chronic disease. Many patients have persistent disease caused by inadequate initial therapy, and underlying localized disease may be present.

Localized and relapsing brucellosis

Localized complications of brucellosis are typically observed in patients with acute disease or chronic untreated infection. Osteoarticular, genitourinary, and hepatosplenic involvement are most common. Cultures of involved tissue sites and serology can be diagnostic. Relapsing brucellosis may be difficult to distinguish from reinfection. Presenting symptoms typically reflect the initial disease; however, these symptoms are more severe. Symptoms typically develop 2-3 months after therapy completion. Culture results are typically positive, and serology may be difficult to interpret, but enzyme-linked immunoassay (ELISA) testing may be more helpful.

Physical findings

Physical findings in patients with brucellosis vary and are nonspecific for the disease. Among the most common findings is hepatosplenomegaly (or isolated hepatomegaly or splenomegaly). Right upper quadrant pain and jaundice may indicate hepatic abscess. Generalized tenderness, rebound tenderness, and sluggish or absent bowel sounds can be expected in patients with peritonitis. Osteoarticular involvement is also common. Focal infection of bones or joints may present with localized abnormal physical findings (eg, swelling, tenderness, and limited motion) in the affected areas. Arthritis, joint effusions, or, in severe cases, costovertebral angle tenderness may be observed. Focal osteomyelitis of the vertebrae, tibia, and, especially, the knee has also been associated with brucellosis infection even in the absence of other significant systemic symptoms. Maneuvers that isolate the sacroiliac joint may cause pain. Focal infection of the genitourinary system may also present with localized abnormal physical findings. Epididymo-orchitis has been described in association with brucellosis; a tender, swollen scrotum with erythema is present in these patients. Urethritis has been reported. Testicular abscess, mimicking tumor, has also been known to occur. Endocarditis may present with new or changing murmurs, and mycotic aneurysms of ventricles, brain, and aorta have been observed. A pericardial rub is present in patients with pericarditis. Although pulmonary complaints are frequently present in patients with brucellosis, physical examination of this organ system almost always yields normal findings.

Neurologic findings vary according to the presentation of neurologic disease and may include the following:

- Acute meningoencephalitis (most common neurologic manifestation) - Depressed level of consciousness, meningeal irritation, cranial nerve involvement, coma, seizure, and respiratory depression
- Meningitis – Nuchal rigidity, Kerning sign, and Brudzinski sign
- Increased intracranial pressure (ICP) or brain abscess – Papilledema, cranial nerve palsy, and focal neurologic deficits
- Peripheral polyradiculoneuropathy - Hypotonia and areflexia in most cases, paraparesis, and an absence of sensory involvement
- Diffuse CNS involvement - Spasticity, hyperreflexia, clonus, extensor plantar response, sensorineural hearing loss, cranial nerve involvement, and cerebellar signs

Cutaneous manifestations develop in 5-10% of patients, are transient and nonspecific, resolve with therapy, and do not alter the prognosis. Lesions reported in association with brucellosis include the following :

- Erythema nodosum, abscesses, and papulonodular eruptions (most common)
- Cutaneous ulcerations
- Impetigo, psoriatic, eczematous, and pityriasis rosea –like lesions
- Macular, maculopapular, and scarlatiniform rashes
- Vasculitic lesions (eg, petechiae, purpura, and thrombophlebitis)

Ocular findings can include the following:

- Uveitis
- Keratoconjunctivitis
- Iridocyclitis
- Nummular keratitis
- Choroiditis
- Optic neuritis
- Metastatic endophthalmitis
- Cataracts.

Complications

Complications are rare in the patient who is treated appropriately, though relapse of infection may occur in 10% of patients. The major risk factor for the development of focal complications is symptom duration greater than 30 days before diagnosis. The most common focal complications fall into the following categories:

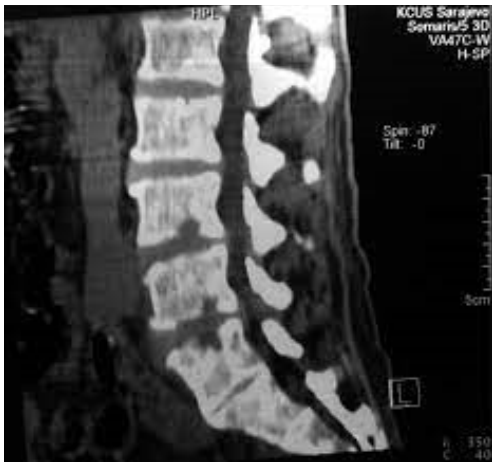
- Osteoarticular
- Hepatobiliary and GI
- Genitourinary
- Neurobrucellosis
- Cardiovascular
- Pulmonary

- Hematologic

Other, less common complications include the following:

- Splenic abscess
- Thyroid abscess
- Epidural abscess
- Uveitis

Osteoarticular



Osteoarticular symptoms affect 20-60% of patients with brucellosis and are the most commonly reported complications; sacroiliitis is the most common (though rarer in children). Spondylitis, arthritis, osteomyelitis, bursitis, and tenosynovitis have been reported. Paraspinal pyogenic complications are often associated with spondylitis, especially in elderly persons. Peripheral joint involvement usually includes the knees, hips, ankles, and shoulders and can be monoarticular or polyarticular.

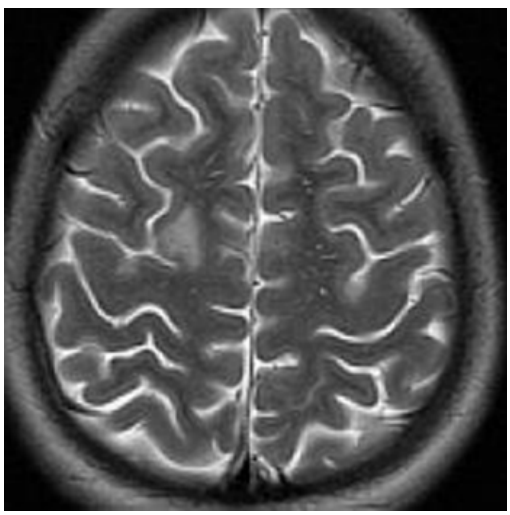
Hepatobiliary

Hepatobiliary complications include hepatitis, hepatic abscess, and acute cholecystitis. The rarely reported GI complications include ileitis, colitis, and spontaneous peritonitis.

Genitourinary

Genitourinary complications usually manifest as orchitis or epididymo-orchitis. Renal involvement is rare, although glomerulonephritis and pyelonephritis have been reported. Infection in pregnant patients is rare and is associated with first-trimester abortions. The frequency of this complication is not substantially different from its frequency when associated with other bacterial infections.

Neurobrucellosis



Neurobrucellosis occurs more frequently in endemic regions and develops in approximately 5% of cases. Meningitis (1-2%) and, less commonly, papilledema, optic neuropathy, radiculopathy, stroke, and intracranial hemorrhage may be seen. Acute meningoencephalitis presents with a prehospital symptom duration of less than 7 days, and clinical findings progress rapidly. With appropriate aggressive therapy, symptoms resolve quickly, and patients are rarely left with residual sequelae. Other forms of neurobrucellosis typically present after at least 3 months of gradual symptoms. After successful therapy, residual deficits are not uncommon; however, they are rarely debilitating.

Cardiovascular

Worldwide, endocarditis occurs in less than 2% of patients with brucellosis; however, in endemic areas, it may affect 7-10% of patients. The aortic valve is affected in 75% of patients, and 50% of affected valves were previously healthy. Endocarditis is responsible for most of the mortality associated with brucellosis. Pericarditis, myocarditis, and mycotic aneurysms of the aorta and cerebral vessels may complicate endocarditis. Primary pericarditis and myocarditis are also reported and have a more favorable outcome.

Pulmonary

Pulmonary complications are reported in 0.3-1% of patients with brucellosis (less commonly in children) and include pneumonia and pleural effusion. These complications are less common in children. Pneumonitis and pleural empyema have been reported.

Hematologic

Hematologic complications are not typically associated with severe sequelae and resolve with appropriate therapy. Reports of disseminated intravascular coagulation (DIC) and the hemophagocytic syndrome have been published. Splenic abscess has been reported.

Differential Diagnoses

Diagnostic Considerations

The signs and symptoms of brucellosis can be nonspecific and can mimic those of many other diseases; therefore, meticulous attention is needed in making the diagnosis and in treating patients. The primary diagnostic pitfall is failure to consider possible *Brucella* infection in a patient with history that suggests a possible source of infection (eg, a farmer, a traveler to an endemic region, or a veterinarian).

In addition to the conditions listed in the differential diagnosis, other problems to be considered include the following:

- Collagen-vascular disease
- Erythema nodosum
- Fever of unknown origin
- Malignancy (eg, lymphoma)
- Rickettsial diseases
- Sacroiliitis
- Vasculitis

Differential Diagnoses

- Abortion Complications
- Acute Epididymitis
- Ankylosing Spondylitis and Undifferentiated Spondyloarthropathy
- Bacterial Pneumonia
- Brain Abscess in Emergency Medicine
- Bronchitis
- CBRNE - Biological Warfare Agents
- Cat Scratch Disease (Cat Scratch Fever)
- Cryptococcosis
- Urinary Tract Infection (UTI) and Cystitis (Bladder Infection) in Females

- Depression and Suicide
- Emergent Management of Subarachnoid Hemorrhage
- Emergent Treatment of Gastroenteritis
- Histiocytosis
- Histoplasmosis
- Epstein-Barr Virus (EBV) Infectious Mononucleosis (Mono)
- Infective Endocarditis
- Influenza
- Leptospirosis
- Lumbar (Intervertebral) Disc Disorder Management in the ED
- Malaria
- Mechanical Back Pain
- Meningitis
- Mycoplasmal Pneumonia
- Osteomyelitis in Emergency Medicine
- Pediatric Chronic Fatigue Syndrome
- Pediatric Mononucleosis and Epstein-Barr Virus Infection
- Spontaneous Bacterial Peritonitis (SBP)
- Thrombotic Thrombocytopenic Purpura (TTP)
- Tuberculosis (TB)
- Tuberculosis of the Genitourinary System
- Tularemia
- Typhoid Fever
- Urinary Tract Infection (UTI) in Males
- Viral Hepatitis
- Viral Pneumonia.

Workup

Laboratory Studies

Complete blood count

A complete blood count (CBC) typically is ordered routinely as part of an evaluation for a patient with potential infectious disease. Leukocytosis is rare in brucellosis, and a significant number of patients are neutropenic. Anemia is reported in 75% of patients (particularly with chronic infection), thrombocytopenia is reported in 40% (secondary to hepatosplenomegaly or from immune thrombocytopenia), and pancytopenia is reported in 6% of patients.

Liver enzymes

A slight elevation in liver enzyme levels is a very common finding. These elevated levels may reflect the severity of hepatic involvement and correlate clinically with hepatomegaly.

Inflammatory markers

Elevations in erythrocyte sedimentation rate (ESR) as well as platelet to lymphocyte ratio, neutrophil to lymphocyte ratio, mean platelet volume have been linked to complicated or organ-specific cases of brucellosis, and may be helpful in indentifying complicated infections for more aggressive treatment.

Culture

Diagnosis of brucellosis is definitive when *Brucella* organisms are recovered from blood, bone marrow, or other tissue. Some *Brucella* species require 5-10% carbon dioxide for primary isolation. Because of the ease of aerosol transmission, any potential *Brucella* specimens should be handled under a biohazard hood. The sensitivity of blood cultures with improved techniques such as the Castaneda bottles is further improved by the lysis-centrifugation technique. With these methods, the sensitivity is approximately 60%. Subcultures are still advised for at least 4 weeks; thus, if brucellosis is suspected, the laboratory should be alerted to keep the cultures for 3-4 weeks, which is not done routinely for most bacterial cultures. Because the reticuloendothelial system holds a high concentration of brucellae, bone marrow culture is thought to be the criterion standard. Sensitivity is usually 80-90%. Any fluid (eg, synovial fluid, pleural fluid, or cerebrospinal fluid [CSF]) can be cultured, but the yield is usually low.

CSF analysis

In patients with neurobrucellosis, analysis of CSF reveals a mild-to-modest lymphocytic pleocytosis of 88-98%. Protein levels are elevated in conjunction with normal glucose levels. CSF cultures are positive for brucellosis less than 50% of the time, but antibody testing of the fluid yields a diagnosis. CSF cultures are indicated for suggested meningitis.

Arthrocentesis

Although significant joint effusion is uncommon, arthrocentesis may occasionally be needed to exclude septic arthritis. The joint aspirate demonstrates an exudative fluid with low cell counts and mononuclear predominance. Patients with brucellosis rarely present with acute monoarticular arthritis.

Serology

Serologic testing is the most commonly used method of diagnosing brucellosis. Repeated serologic testing is recommended if the initial titer is low. The tube agglutination test, developed by Bruce, measures antibodies against smooth lipopolysaccharide (LPS); it remains the most popular test tool for the diagnosis of brucellosis. The 2-mercaptoethanol test detects immunoglobulin G (IgG), and titers higher than 1:80 define active infection. A high IgG antibody titer or a titer that is higher after treatment suggests persistent infection or relapse. Other tests, such as tray agglutination (TAT) and modified TAT, are also popular. Titers higher than 1:160 in conjunction with a compatible clinical presentation are considered highly suggestive of infection. Titers higher than 1:320 are considered to be more specific, especially in endemic areas. Seroconversion and evolution of the titers can also be used for diagnosis. The shortcomings of agglutination tests test include potential cross-reactivity with IgM of other organisms such as *Francisella tularensis, Salmonella urbana, Yersinia enterocolitica* serotype O9, *Vibrio cholerae, Afipia clevelandensis,* and some other bacteria. Prozone phenomenon may occur secondary to hyperantigenemia, possibly leading to false-negative results. Accordingly, routine dilution of sera (typically beyond 1:320) is necessary to avoid this problem. Enzyme-linked immunosorbent assay (ELISA) typically uses the cytoplasmic proteins as antigens and measures IgM, IgG, and IgA, allowing better interpretation, especially in cases of brucellosis relapse. This is because antibodies against LPS, which are used in agglutination tests, might persist for longer periods and are believed to yield higher sensitivity and specificity. ELISA of CSF also helps diagnose neurobrucellosis. Because levels should decrease with effective treatment, ELISA is also helpful in follow-up.

Rapid point-of-care assays

Point-of-care assays are available that offer fast and accessible diagnostic capabilities, especially in areas were special laboratory resources are lacking.

Polymerase chain reaction

Polymerase chain reaction (PCR) tests have been developed for the detection and rapid diagnosis of *Brucella* species in human blood specimens. Two major genetic targets are the *Brucella* gene *BCSP31* and the 16S-23S rRNA operon. The 16S-23S rRNA operon has been shown in studies to be more reliable in terms of sensitivity but is not yet widely used in clinical practice and needs more standardization. Possible applications would include evaluating cases of relapse and monitoring response to therapy. Other promising tests include nested PCR, real-time PCR, and PCR-ELISA, but the clinical roles for all of

these tests remain to be defined. ref50}

Urinalysis and urine culture

Urinalysis, urine culture, sensitivity testing, or a combination thereof may be indicated in the presence of symptoms of urinary tract infection (UTI). The most likely finding is a sterile pyuria, similar to that seen with tuberculosis. Urine cultures may be helpful; the organism grows from the urine if the genitourinary tract is infected.

Radiography

A chest radiograph should be obtained if respiratory symptoms are present or if a source of infection is not apparent. Radiographic findings are typically absent in brucellosis, even in patients with prominent respiratory symptoms. Findings that may be observed in patients with active pulmonary involvement include hilar and paratracheal lymphadenopathy, pulmonary nodules, pleural thickening, and pleural effusion. Spinal radiographic findings in patients with osteoarticular disease occur later in the course of illness, usually 2-3 weeks after the onset of symptoms. In patients with sacroiliitis, the most commonly observed abnormalities include blurring of articular margins and widening of the sacroiliac spaces. Spondylitis-related abnormalities include anterosuperior vertebral angle epiphysitis, spinal straightening, narrowing of the intervertebral disc spaces, end-plate sclerosis, and osteophytes.

Other Imaging Studies

Ultrasonography

Echocardiography is used to evaluate for possible endocarditis. The primary site of vegetation is the aortic valve, with the sinus of Valsalva most commonly affected, followed by the mitral valve. Mycotic aneurysms of the aorta or carotids may be observed on duplex arteriography. Use of ultrasonography to diagnose testicular abscess from brucellosis has been reported; low-resistance flow appears to be characteristic for these tumors.

Radionuclide scintigraphy

Radionuclide scintigraphy is more sensitive for revealing skeletal abnormalities, especially early in the disease, when standard radiographic findings are usually normal. This modality may be especially helpful in distinguishing hip involvement from sacroiliitis. To facilitate prompt diagnosis, radionuclide scintigraphy also may have a role in screening for new-onset brucellosis and musculoskeletal symptoms.

Computed tomography

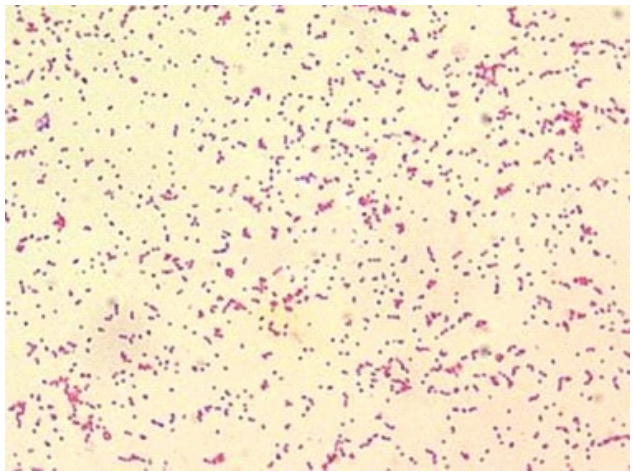
In patients with altered mental status or focal neurologic deficits, cranial computed tomography (CT) is warranted. Although the CT scan is often normal, it may reveal evidence of acute or chronic *Brucella* leptomeningitis, subarachnoid hemorrhage, or cerebral abscess.

Biopsy

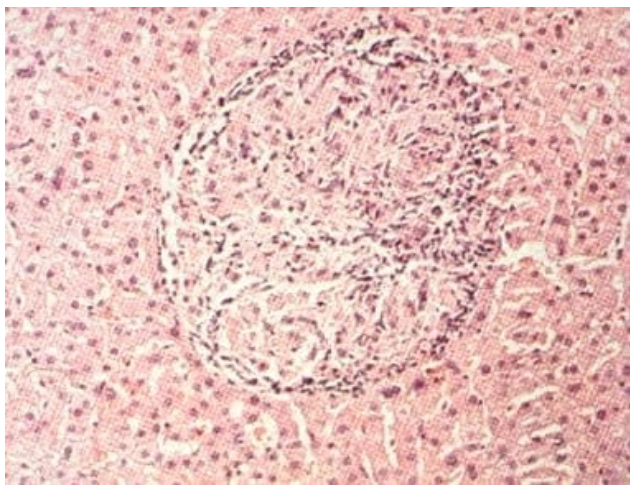
Bone marrow aspiration and biopsy may be required to establish a diagnosis in certain patients. Bone marrow examination may reveal erythrophagocytosis. Microangiopathic hemolytic anemia, thrombocytopenic purpura, and Coombs-positive hemolytic anemia have been reported in brucellosis. Percutaneous liver biopsy may be needed in the patient with liver granulomas to obtain a specimen for diagnosis. Analysis of liver biopsy specimens may reveal granulomatous hepatitis and hepatic microabscesses.

Histologic Findings

Histologic findings in brucellosis usually include mixed inflammatory infiltrates with lymphocytic predominance and granulomas (in up to 55% of cases) with necrosis.



Brucella species are poorly staining, small gram-negative coccobacilli (0.5-0.7 × 0.6-1.5 µm) and are seen mostly as single cells with an appearance resembling "fine sand."



Well-formed hepatic granuloma from patient with brucellosis

Treatment & Management

The goal of medical therapy in brucellosis is to control symptoms as quickly as possible in order to prevent complications and relapses. Initial care for brucellosis is supportive. Given the nonspecificity of patient complaints, a diagnosis of brucellosis in the emergency department (ED) is unlikely. With an appropriate history, an astute clinician may suspect it. Appropriate precautions (eg, mask, gloves, and eye protection) should be taken for respiratory procedures or handling body fluids. Specimens from the patient should be handled in the laboratory under biosafety level III conditions. Multidrug antimicrobial regimens are the mainstay of therapy because of high relapse rates reported with monotherapeutic approaches. The risk of relapse is not well understood; resistance is not a significant issue in treating brucellosis. Depending on what other systems are involved, more specialized care may be needed. Transfer to another facility depends on the needs of the patient. Because most patients do not require highly specialized interventions, the need to transfer should not be frequent. Personnel involved in the transfer should maintain respiratory and contact precautions, and the vehicle should be decontaminated after transport as needed.

INTERPRETATION

FEVER/ PYREXIA OF UKNOWN ORIGIN

Diagnostic Considerations

Approximately 5-15% of patients with fever of unknown origin (FUO) remain undiagnosed, even after extensive evaluations.

Hepatobiliary infections

Acute cholecystitis and gallbladder empyema can lead to a diagnosis of FUO because of the lack of right upper quadrant pain or jaundice, especially in elderly patients.

Osteomyelitis

The most common reason for misdiagnosis of osteomyelitis is the failure to consider the disease in a patient who is febrile with musculoskeletal symptoms.

Parasitic infections

If the physician is unaware of a history of recent travel to an endemic area and if the fever pattern is non synchronized, malaria can be missed as a cause of fever.

Drug fever

A history of allergy, skin rashes, or peripheral eosinophilia often is absent in cases of drug fever.

Tuberculosis

Tuberculosis (TB) usually is considered in the differential diagnoses; however, several factors may prevent a prompt diagnosis of TB. Miliary TB may initially manifest as constitutional symptoms that lack localizing signs.

Collagen-vascular and autoimmune diseases

Consider PAN, RA, and mixed connective-tissue diseases in patients with FUO, because of the potential for nonspecific presentations in these diseases. Rheumatic fever can be difficult to diagnose, because it is rare in the developed world.

Conditions to consider in the diagnosis of FUO/PUO

More than 200 conditions may cause FUO and include the following, as well as the disorders in the Differentials subsection, below:

- Abdominal Abscess
- Actinomycosis
- Acute Lymphoblastic Leukemia
- Acute Myelogenous Leukemia
- Adenoviruses
- Adrenal Carcinoma
- Adrenal Insufficiency
- Amebiasis
- Amebic Hepatic Abscesses
- Atrial Myxoma
- Atypical Mycobacterial Infection
- Bacillary Angiomatosis
- Bacteroides Infection
- Bartonellosis
- Blastomycosis
- Brain Abscess
- Brucellosis
- California Encephalitis
- Campylobacter Infections
- Candidiasis
- Carcinoid Tumor, Intestinal
- *C burnetii* infection
- Chagas Disease (American Trypanosomiasis)
- Cholangitis
- Cholecystitis
- Choledocholithiasis
- Chronic Bacterial Prostatitis
- Chronic Lymphocytic Leukemia
- Chronic Mesenteric Ischemia
- Chronic Myelogenous Leukemia
- Clostridial necrotizing fasciitis
- Colon Cancer, Adenocarcinoma
- Coxsackieviruses
- Cryptococcosis
- Cytomegalovirus
- Cytomegalovirus Colitis
- Dengue Fever
- Diabetic Ulcers
- Drug Fever
- Eastern Equine Encephalitis
- Echoviruses
- Emphysematous Pyelonephritis
- Empyema, Gallbladder
- Empyema, Pleuropulmonary
- Enteroviruses
- Eosinophilic Pneumonia
- Eosinophilic Toxocariasis
- Epididymal Tuberculosis
- Epididymitis
- Epidural Abscess
- Erythema Multiforme (Stevens-Johnson Syndrome)
- Factitious Fever
- Gallbladder Gangrene
- Gastroenteritis, Viral
- Giardiasis
- Graves Disease
- Hairy Cell Leukemia
- Hepatitis A-E
- Hepatoma
- Herpes Simplex

- Histoplasmosis
- Human Immunodeficiency Virus
- Human Herpesvirus Type 6
- Hypersensitivity Pneumonitis
- Hyperthyroidism
- Inflammatory Bowel Disease
- Intra-abdominal Sepsis
- Japanese Encephalitis
- Kikuchi Disease
- Legionnaires Disease
- Leishmaniasis
- Leptospirosis
- Leukocytoclastic Vasculitis
- Libman-Sacks Endocarditis
- Listeria Monocytogenes
- Liver Abscess
- Lung Abscess
- Lymphocytic Choriomeningitis
- Lyssavirus Infection
- Malaria
- Malassezia furfur Infection
- Malignant histiocytosis
- Mastocytosis, Systemic
- Mediterranean Fever, Familial
- Mediterranean Spotted Fever
- Meningococcemia
- Miliary Tuberculosis
- Mucormycosis
- Mycoplasma Infections
- Naegleria Infection
- Neuroleptic Malignant Syndrome
- Nocardiosis
- Nonarticular Rheumatism/Regional Pain Syndrome
- Nonbacterial Prostatitis
- Norwalk Virus
- Onchocerciasis
- Osteomyelitis
- Pancreatitis, Acute
- Pelvic Inflammatory Disease
- Pericholangitis
- Pharyngitis, Viral
- Pneumonia, Viral
- Prostatic Abscess
- Psittacosis
- Q Fever
- Rat-bite Fever (S minor)
- Rhinocerebral Phycomycosis
- SARS-Covid 19
- Sphenoid Sinusitis
- Thrombophlebitis
- Trypanosoma Infection
- West Nile Virus
- Zika Virus.

Differential Diagnoses

- Acute Pericarditis
- Appendicitis
- Arenaviruses
- Aspergillosis
- Cat Scratch Disease (Cat Scratch Fever)
- Celiac Disease (Sprue)
- Constrictive Pericarditis
- Gout and Pseudogout
- Graft Versus Host Disease (GVHD)
- Myocarditis.

TROUBLESHOOTING

Fever of Unknown Origin (FUO/PUO) Workup

Laboratory Studies

While a workup of FUO should emphasize clinical clues, the following, if not already performed, are essential laboratory and imaging tests that are of value in eliciting further diagnostic direction:

- Complete blood cell (CBC) count with white blood cell (WBC) differential
- Peripheral blood smear
- Complete metabolic panel (CMP; provides data on electrolytes, glucose, acid-base, renal, liver, protein status)
- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR)
- Urinalysis (used to detect glomerulonephritis, occult hematuria; pyuria is insensitive for detecting urinary tract infection in the absence of suggestive symptoms, as asymptomatic bacteriuria is common)
- Blood cultures, preferably 3 blood draws from separate sites, performed at different times
- HIV serology
- Hepatitis A and B serology, and if epidemiologically applicable, Hepatitis E serology
- Tuberculosis screening tests – Purified protein derivative (PPD, or Mantoux test); interferon gamma release assays (IGRA)
- Posteroanterior and lateral chest radiography.

Beyond the above essentials in early screening, some would add antinuclear antibody titers, rheumatoid factor, and thyroid stimulating hormone (TSH) and thyroxine level in diagnosing certain conditions (lupus, RA, thyroiditis, hyperthyroidism). Their diagnostic accuracy is limited in other autoimmune and collagen vascular diseases. Further examinations should be guided by historical and physical diagnostic clues, as well as clues from the initial results of the above.

HIV serology

If any test should be routinely included in the evaluation of FUO, HIV antigen-antibody assay should. Antigen-antibody assay results are positive early in infection, thus eliminating need for HIV viral load screening because of lag in antibody seroconversion.

C - reactive protein

Elevated CRP suggests an infectious or inflammatory process, but does not eliminate malignancy.

Erythrocyte sedimentation rate

An ESR of more than 100 seconds in the absence of anemia may indicate giant cell arteritis, multiple myeloma, or osteomyelitis. A very low ESR with myalgias suggests trichinosis.

Complete blood count

Eosinophilia may suggest polyarteritis nodosa, drug fever, or visceral leishmaniasis. Acute drop in hemoglobin or hematocrit may suggest occult hemorrhage or hematoma (often retroperitoneal).

Complete metabolic profile

Alkaline phosphatase elevation suggests lymphoma or granulomatous hepatitis. Transaminitis may result from multiple causes. Elevated total protein or calcium (look for monoclonal gammopathy) may suggest multiple myeloma.

Urinalysis

Hematuria may indicate renal cell carcinoma, tuberculosis, endocarditis, brucellosis, lymphoma, or periarteritis nodosa. Asymptomatic pyuria and bacteriuria are common with advancing age and comorbidities, and these findings may offer little diagnostic direction. Normal urinalysis or urine culture results do not necessarily suggest or eliminate perinephric abscess. Approximately 30% of patients with perinephric abscess have normal urinalysis results, and up to 40% have sterile urine cultures.

Blood cultures

Blood cultures for aerobic and anaerobic pathogens are essential in the evaluation; however, no more than 6 sets of blood cultures are required. Sampling 2-3 peripheral blood samples may suffice given modern culture techniques.

Tuberculosis screening

PPD or Mantoux screening is inexpensive and sensitive but requires placement by clinical staff and interpretation 48-72 hours later of induration size, a type IV hypersensitivity reaction (indicating prior tuberculosis exposure). Interferon gamma release assay (IGRA) offers higher sensitivity and, where readily available and quickly processed, faster turnaround.

Laboratory clues to specific causes of FUO

Anemia is an important finding and suggests a serious underlying disease. Suspect herpesvirus infection if the patient has lymphocytosis with atypical cells. Leukocytosis with an increase in bands suggests an occult bacterial infection, as well as occult hemorrhage, hematoma, or thromboembolic process. Diagnose malaria and spirochetal diseases with the aid of direct examination of the peripheral blood smear; however, repeated examinations by an experienced technologist are often necessary. With relapsing fever/spirochetal diseases, it is best to obtain blood sample during febrile period for highest probablity of spirochetemia and direct observation. Preleukemic states may not manifest in the peripheral blood smear, and bone marrow aspirate may not reveal the correct diagnosis; bone marrow biopsy may be necessary for diagnosis. Adult-onset Still disease often is difficult to diagnose. Laboratory abnormalities include pronounced leukocytosis, an elevated erythrocyte sedimentation rate (ESR), anemia, and abnormal liver function test results. Among solid tumors, renal cell carcinoma is most commonly associated with FUO, with fever being the only presenting symptom in 10% of cases. Hematuria may be absent in approximately

40% of cases, whereas anemia and a highly elevated sedimentation rate are common. Laboratory findings in giant cell arteritis (GCA) include an elevated ESR, mild to moderate normochromic normocytic anemia, elevated platelet counts, and abnormal liver function test results (25% of cases). Perform a biopsy of a temporal artery to obtain a definitive diagnosis. Pathologic review shows vasculitis and a mononuclear cell infiltrate. At least one liver function test result usually is abnormal in an underlying disease that originates in the liver or a disease that causes nonspecific alterations of the liver (eg, granulomatous hepatitis).

Tissue analysis and cultures

Assays, serology, and cultures

Aside from HIV screening, other assays, serology, and cultures should be directed by findings of the history, physical, and laboratory screening, as well as clinical reevaluation for more diagnostic clues. The specifics of testing for individual conditions is deferred to other more detailed sources.

Imaging Studies

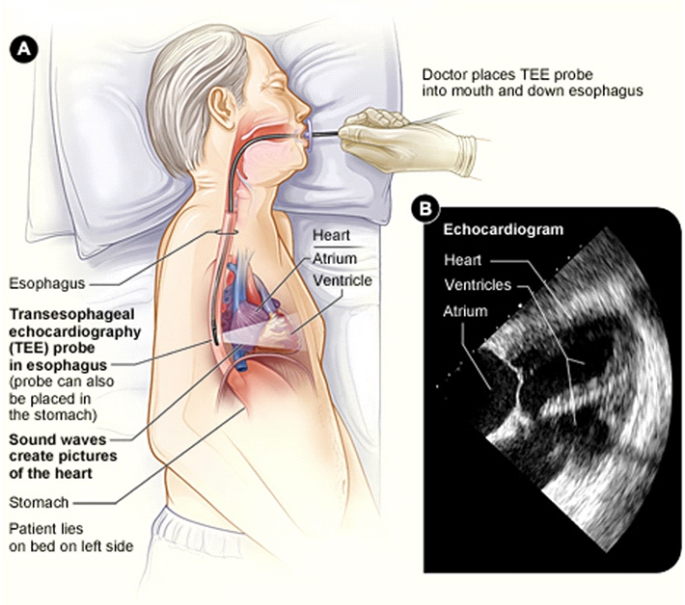
Chest radiography

Routinely perform chest radiography. Posteroanterior and lateral chest radiography usually is readily available and relatively inexpensive. It may rapidly detect abnormalities missed on physical examination, and may direct further diagnostic imaging with computed tomography (CT) of the thorax.

Thoracic CT angiography

Thoracic CT angiography is more sensitive than ventilation-perfusion scanning when pulmonary emboli are suspected in spite of negative findings on venous ultrasonography of the extremities. Arteriography demonstrates small and large aneurysms and focal constrictions between dilated segments in polyarteritis nodosa.

Echocardiography

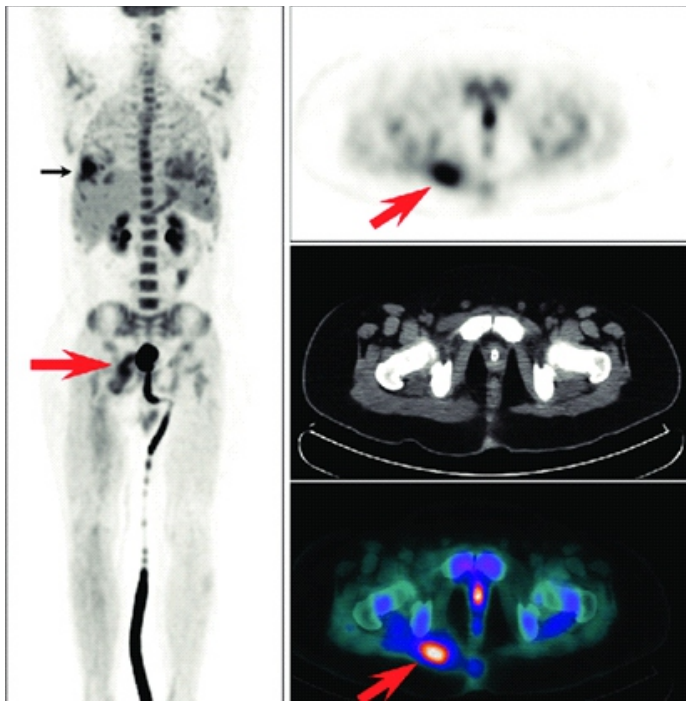


Echocardiography is highly sensitive in diagnosing endocarditis, particularly when transesophageal echocardiography is available. Culture-negative endocarditis is reported in 5-10% of endocarditis cases. Prior antibiotic therapy is the most common reason for negative blood culture results.

CT scanning of the abdomen and pelvis

CT scanning of the abdomen and pelvis with intravenous and oral contrast is useful in the setting of hepatosplenomegaly looking for adenopathy, intraabdominal or psoas muscle hematoma or abscess, perinephric abscess, cholecystitis, or neoplasia. Plain abdominal films and ultrasonography are relatively insensitive in the diagnosis of FUO. In patients with hepatobiliary infections, cholangitis can occur without local signs and with only mildly elevated or normal findings on liver function tests.

FDG-PET/CT whole-body scanning



Positron emission tomography (PET) scanning alone once was fraught with excessive false-positive findings; however, PET combined with CT improves diagnostic capabilities, especially as the causes of FUO have evolved in the past decade. F-fluorodeoxyglucose positron emission tomography (FDG-PET), in which radiolabeled glucose marks foci of increased glucose metabolism, has been used successfully in oncology diagnostics and also can be used to diagnose infectious and noninfectious inflammatory foci. Recent studies recommend using FDG-PET early in the workup of FUO and suggest that including FDG-PET/CT yields a correct diagnosis in 60% to more than 80% of cases. Furthermore, the time to diagnosis may be shortened and invasive procedures reduced, potentially leading to reduced costs and morbidity. Nonetheless, the possibility of false-positive results should be kept in mind.

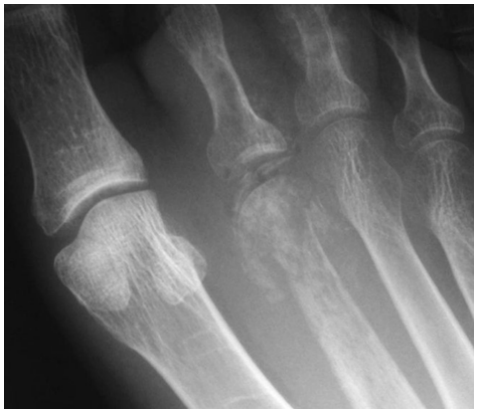
Radionucleotide studies

Radionucleotide studies using gallium citrate are used to detect chronic inflammation and may be more sensitive in detecting occult abscesses, neoplasms, or soft-tissue lymphomas in FUO of more than 2 weeks' duration. Indium WBC scan, using granulocytes labeled with indium In 111 (In), can be cumbersome and often insensitive in chronic inflammatory states.

Bone scanning

Whereas plain radiographs may not show changes for weeks after the

onset of infection, technetium bone scan may be a more sensitive method for documenting skeletal involvement when osteomyelitis is suspected. Magnetic resonance imaging (MRI) is considered the criterion standard for detection of acute osteomyelitis and delineating structural abnormalities; however, it is less sensitive in the setting of chronic osteomyelitis and prosthetic joint infection. While potentially a greater cost upfront, positron emission tomography-computed tomography (PET-CT) full-body scans are increasingly recognized as useful early in efficiently localizing abnormalities and may save other healthcare costs in the FUO workup. PET-CT is especially sensitive in localizing and detecting small foci of inflammation and metabolic activity. It is particularly superior to MRI and other nuclear imaging studies in localizing foci of osteomyelitis of the hip, vertebrae, or prosthetic devices, as well as endovascular graft infection, neoplasia, and vasculitides.



Other Tests

Naproxen test

Simple, noninvasive, and inexpensive, a naproxen test may rapidly screen out infection versus neoplastic disease and significantly narrow the differential diagnoses. In this test, naproxen sodium 250 mg is given orally every 8 hours for 3 days. A sharp decline or resolution in fever within 24 hours directs the workup away from infection and suggests a neoplastic disorder.

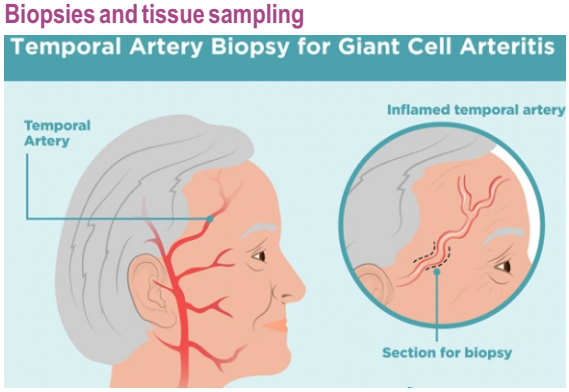
Procedures

FUO evaluations are best performed from least invasive to more invasive testing.

Endoscopy

Perform an endoscopic examination of the upper and lower gastrointestinal tract, including retrograde cholangiography when indicated or when searching for Crohn disease, Whipple disease, biliary tract disease, and gastrointestinal tumors. Crohn disease is the most common gastrointestinal cause of FUO. Diarrhea and other abdominal symptoms occasionally are absent, particularly in young adults.

Biopsies and tissue sampling



Obtain cultures for bacteria, mycobacteria, and fungi in all normally sterile tissues and liquids that are biopsied. This may include cerebrospinal fluid (CSF), pleural or peritoneal fluid, and fluid from the liver, bone marrow, and lymph nodes. Biopsies are easily performed in enlarged accessible lymph nodes, other peripheral tissues, and bone marrow. Superficial enlarged lymph nodes of highest yield on biopsy include posterior cervical, supraclavicular or infraclavicular, and epitrochlear nodes. Deep nodes of highest yield are the hilar, mediastinal, or retroperitoneal lymph nodes. Bone marrow biopsy is of highest yield with unexplained abnormality of the CBC count (hematologic malignancy) and granulomatous disease such as sarcoidosis, tuberculosis, or histoplasmosis. Liver biopsy rarely yields helpful data in patients without abnormal liver function test results or abnormal liver findings (observed on CT scan or ultrasonography). Liver biopsy may be necessary to characterize granulomatous or autoimmune hepatitis. The decision to biopsy is more difficult if it entails an exploratory surgical procedure (eg, laparotomy). This is rarely indicated (eg, when imaging techniques are nondiagnostic and an intra-abdominal source is suspected), particularly considering the generally benign course of FUO that remains undiagnosed after extensive workup.

Arterial biopsy rarely is associated with hematoma, ischemic complications, or nerve damage, given that nerves and vessels often follow a similar course. This may be warranted, however, for the diagnosis of polyarteritis nodosa and giant cell arteritis, as these conditions may be disabling or life-threatening if left untreated; these are among the few conditions associated with an erythrocyte sedimentation rate of 100 mm/hour or greater. Biopsy of small- or medium-sized arteries demonstrate white blood cell infiltrate in polyarteritis nodosa. Temporal artery biopsy is necessary for definitive diagnosis of giant cell arteritis, provided a sufficient length of artery is excised.

Pyrexia (fever) of unknown origin presents the common symptom to clinicians and as a result to laboratorians. This is usually resolved through multiple testing based on principle of exclusion. This leads in a lapse of significant time in diagnosis of the root cause and resultant delay in dispensing correct therapeutic intervention. Simultaneous testing of infectious targets is the correct and appropriate approach in such cases.

While still hovering around the issue of FUO – how do we make it FKO or fever of known origin? Onslaught of monsoons in the subcontinent brings along with three specific fevers, viz., **DENGUE, ENTERIC FEVER (Typhoid)** and **MALARIA**.

So, an integrated test for detection of earliest markers of Malaria, Typhoid and Dengue infection is the need of an hour.

What a boon it would be if one had access to an integrated testing system that diagnoses all three in one go.

More often than not, the request for the three fevers diagnosis is mentioned on the same requisition slip, hence, a three in one system would be the most ideal. Three different kits from three different boxes would be now a thing of the past!

BOUQUET

In Lighter Vein

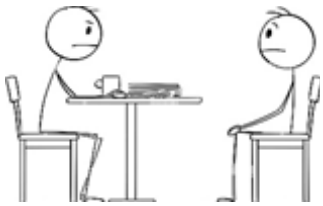
Boss: I always tell new hires, don't think of me as your Boss…

Employees in thought: Think of me as your friend who can fire you simple.

A young man was applying for a job in a big company.

"I'm sorry," said the personnel manager, "but the firm is overstaffed; we have more employees now than we really need."

"That's all right," replied the young man, undiscouraged, "the little bit of work I do won't be noticed anyway."



I went to work today and saw a memo on my desk from the boss about sick days:

We will no longer accept a doctor statement as proof of sickness.

If you are able to go to the doctor, you are able to come to work.

Wisdom Whispers

"Successful people are not gifted; they just work hard, then succeed on purpose."

❀

"The only thing standing between you and outrageous success is continuous progress."

❀

"Success is no accident. It is hard work, perseverance, learning, studying, sacrifice and most of all, love of what you are doing or learning to do."

❀

"You never know what's around the corner. It could be everything. Or it could be nothing. You keep putting one foot in front of the other, and then one day you look back and you've climbed a mountain."

Brain Teasers

1. **What is the most common way Brucella is transmitted to humans?**
   A. Ingestion of contaminated food or water
   B. Inhalation of contaminated air
   C. Direct contact with infected animals
   D. All of the above

2. **Which of the following is NOT a way to prevent Brucella infection in animals?**
   A. Vaccination
   B. Quarantine of infected animals
   C. Use of antibiotics in infected animals
   D. Good hygiene and sanitation practices

3. **Which of the following is NOT a common symptom of Brucella infection in animals?**
   A. Reduced milk production in cows
   B. Abortion in pregnant animals
   C. Joint pain in dogs
   D. Respiratory distress in pigs

4. **Which of the following is a common complication of untreated Brucella infection in humans?**
   A. Chronic fatigue syndrome
   B. Liver failure
   C. Kidney failure
   D. Heart attack

ANSWER: 1: D, 2: C, 3: C, 4: B

Diagnosis of fever!

Why Wait?

PyroCHECK™

Integrated test for earliest markers of -
● Malaria ● Dengue ● Typhoid

- **Single integrated test system for Pyrexia** - Detection of Malaria Pf and Pv, Typhoid - IgM and Dengue NS 1 antigen in a single test system.
- **Suitable for complete fever profile test prescription** – Faster treatment decision by clinician.
- **Integrated testing system minimize the procedural and labelling error as single labelling for three tests i.e. Malaria, Dengue and Typhoid** – Easy to handle less test turn-around time.
- **Well suited for point of care testing, as well as pathological lab testing** - Uses whole blood as specimen.

Performance of PyroCHECK™

Diagnostics parameters	Sensitivity %	Overall Specificity %
Malaria *P. Falciparuam* (HRP-2)	100	98.53
Malaria *P. Vivax* (pLDH)	100	
Typhoid (*S. Typhi* IgM)	94	
Dengue (NS1)	98.6	

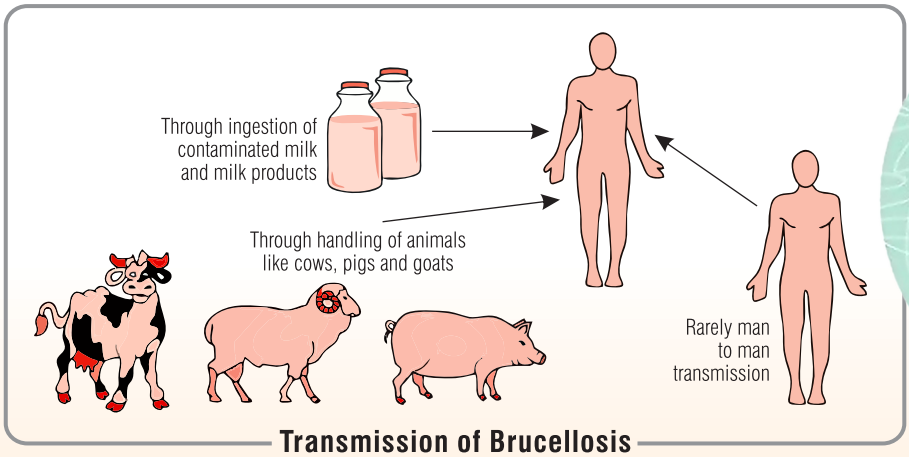
*Data on file: Tulip Diagnostics (P) Ltd. (Comparison with ELISA)

For Immediate Diagnosis of Fever!

Printed and published by D.G. Tripathi, Edited by Dr. Ramnik Sood, M.D. (Path.) for and on behalf of Tulip Diagnostics Private Ltd., Gitanjali, Tulip Block, Dr. Antonio Do Rego Bagh, Alto Santacruz, Bambolim Complex Post Office, Goa - 403 202, INDIA.
E-mail: sales@tulipgroup.com Website: www.tulipgroup.com

BRUCELLOSIS

- Brucellosis is transmited to humans via livestock and contaminated dairy foods.
- Farmers, shepherds, veterinarians and butchers are at increased risk of Brucellosis infection.
- Diagnosis is recommended in Pyrexia of Unknown origin (PUO).



Transmission of Brucellosis

Diagnosing Brucellosis in humans and animals is pivotal for safeguarding public health and fostering food safety.

Tulip's Brucellosis Reagents for Humans & Animals

Brucel-RB (5mL)

Reagent with Rose Bengal Dye calibrated against 2nd International preparation of Anti-Brucella abortus for initial screening of infection caused *by B. abortus/B. melitensis* on slide and tube.

Brucel-A and Brucel-M (5mL)

B. abortus and *B. melitensis* antigen suspensions for detection of antibodies to respective Brucella species. Suitable for slide and Tube test.

Brucellosis Diagnosis in Humans & Animals!

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E-mail: sales@tulipgroup.com Website: www.tulipgroup.com