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Artigo

The worldwide spread of Crimean Congo hemorrhagic fever orthonairovirus and Q fever: risk factors and implications for control strategies of a zoonotic disease

A propagação mundial da febre hemorrágica da Crimeia-Congo ortonairovírus e febre Q: fatores de risco e implicações para estratégias de controle de uma doença zoonótica

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Abstract: Crimean Congo hemorrhagic fever (CCHF) orthonairovirus and Q fever are zoonotic infections. CCHF is the dominant tick borne viral infection among livestock, with a serious threat to humans as well. Wide host range and asymptomatic traits has made infection eradication difficult. In addition, low infectious dose of the virus has made it a highly pathogenic agent. CCHF is recognized as a threat to public health and public health services for its epidemic potential, high fatality rate (up to 40%), its potential for nosocomial outbreaks and difficulties in treatment, prevention and control. Q fever is also a serious health threating disease. Knowledge of causative agent (*Coxiella burnetii*) remains limited until today. The rate of CCHF and Q fever as zoonotic infections has remained high in most of regions worldwide. Hence implementation of accurate control strategies can help prevent its spread. Use of ticks' repellants, control of livestock and wildlife movements and multinational policies are also essential in this regard. Noticeably, it is necessary to establish and empower the international surveillance fulfills to better predict, investigate and control these infectious diseases, improve the international public health infrastructure, develop enhanced international guidelines, and recommendations to improve the international capabilities toward restriction of disease outbreaks with adequate medical and scientific resources and expertise. To predict and monitor the CCHF and Q fever, regional rather than countrywide scale cooperation is necessary. Immigration/travel also remains an important factor influencing the spread of these agents.

Key words: Crimean Congo hemorrhagic fever, Q fever, Zoonoses, control strategies

Resumo: A febre hemorrágica do Congo da Crimeia (CCHF) ortonairovírus e a febre Q são infecções zoonóticas. A CCHF é a infecção viral transmitida por carrapatos dominante entre o gado, com uma séria ameaça também para os seres humanos. A ampla gama de hospedeiros e as características assintomáticas dificultam a erradicação da infecção. Além disso, a baixa dose infecciosa do vírus o tornou um agente altamente patogênico. A CCHF é reconhecida como uma ameaça à saúde pública e aos serviços de saúde pública por seu potencial epidêmico, alta taxa de letalidade (até 40%), seu potencial para surtos nosocomiais e dificuldades no tratamento, prevenção e controle. A febre Q também é uma doença grave que ameaça a saúde. O conhecimento do agente causador (Coxiella burnetii) permanece limitado até hoje. A taxa de CCHF e febre Q como infecções zoonóticas permaneceu alta na maioria das regiões do mundo. Portanto, a implementação de estratégias de controle precisas pode ajudar a evitar sua disseminação. O uso de repelentes de carrapatos, o controle dos movimentos de gado e animais selvagens e políticas multinacionais também são essenciais nesse sentido. Notavelmente, é necessário estabelecer e capacitar a vigilância internacional para melhor prever, investigar e controlar essas doenças infecciosas, melhorar a infraestrutura internacional de saúde pública, desenvolver diretrizes internacionais aprimoradas e recomendações para melhorar as capacidades internacionais de restrição de surtos de doenças com recursos e conhecimentos médicos e científicos. Para prever e monitorar a CCHF e a febre Q, é necessária uma cooperação em escala regional e não nacional. A imigração/viagens também continua a ser um fator importante que influencia a disseminação desses agentes.

Palavras-chave: Febre hemorrágica da Crimeia-Congo, febre Q, Zoonoses, estratégias de controle

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Introduction

Crimean fever (Crimean Congo hemorrhagic fever *orthonairovirus*, CCHF) and query (Q) fever are causative agents of zoonotic infections that can be transmitted by arthropods (1). They are highly-priority pathogens identified on the WHO R&D Blueprint because of their high case fatality rate, potential for nosocomial outbreaks and difficulties in treatment and prevention (2, 3). The agents have a potential transmission, sever pathogenesis and significant outbreaks in some areas and countries including Iran, and also there is a scarce of published data regarding the both infections status in developing countries. For these reasons it is necessary to have a comprehensive and systematic discussion of the both infections.

Background and history

CCHF is an acute febrile, zoonotic infection, known by other names such as Karakhalak, Khunymuny, Hungribta and also has further names worldwide (4,5). The first described case of the infection was in Crimea region in 1940 (4). In 1944, during the World War II, the infection became widespread in the Crimean Peninsula, and caused death of more than 200 villagers and soldiers (7), afterword, the infection acquired a name of 'Crimean hemorrhagic fever'. In 1956 the virus firstly isolated in Congo and named 'Congo virus'; then after the two names converged as CCHF in 1969 (5).

The causative agent of CCHF is arbovirus (belonging to Nairovirus genus of Bunyaviridae family), is placed in arthropod-borne viruses group. Similar to other Nairovirus members (Bunyavirales order, Nairoviridae family and Orthonairovirus genus). CCHF is an enveloped virus with a single-stranded RNA that consists of 3 parts, the small part (S), the middle part (M), and the large protein (L), which encode for the nucleocapsid protein (NP), the envelope glycoproteins G1 and G2 and an RNA-dependent polymerase, respectively.

Epidemiology

The CCHF is considered as the predominant tick-borne infection in humans from animal sources (9). Human is known as the major host for the CCHF virus, and the disease is associated with an acute febrile illness followed

by a fatal hemorrhagic syndrome with a mortality rate of more than 50%, while in livestock animals the infection is subclinical and lasts from several days to weeks. The geographical distribution of the CCHF relies on the carrier ticks (*Hyalomma* spp).

The disease has been reported from around 30 countries including Africa (Uganda, Sudan, Nigeria, Mauritania, Senegal, South Africa), Eastern Europe (Bulgaria, Yugoslavia, Hungary, Turkey and Greece), the Middle East (Iraq, Pakistan, Afghanistan and Iran), India and West China (10). The highest incidence of this infection occurs in Iran during the warm seasons from late March to late September (related to tick's multiplication and maturity season). Several studies have been performed regarding the geographical distribution of the CCHF in several Iran provinces, such as Sistan, Baluchistan, Isfahan, Fars, Tehran, Khorasan and Khuzestan, and studies indicated a high rate of the infection in these areas.

The CCHF virus is primarily transmitted by hard ticks, such as the *Hyalomma* species in nature, but the infection is also capable of being transmitted by other ticks such as *Amblyomma, Dermacenter, Haemophysalis, Rhipicephalus, Boophilus* and *Ixodes* species. There is transovarion and Transstadial transmission of the CCHF virus through different stages of the tick development (6). The predominant route of infection acquired from *Hyalomma* spp. ticks which in turn get the virus from small vertebrates. Once infected, the tick will remain carrier for the virus throughout the evolutionary stages, and the adult tick become infective for large vertebrates like livestock. Other ways of CCHF transmission to humans include bite of contaminated tick, contact with crushing ticks, contaminated blood, contaminated secretions, tissues, carcass, breathing in contact with contaminated people or livestock, aerosol-generating medical procedures and nosocomial transmission. Major people at risk of this infection include: livestock breeders and farmers, slaughterhouse workers, veterinarians and health care staff (hospitals).

Several studies have been conducted about the spread of the infection in different regions in Iran through the period 2000-2014, in which, there is a high prevalence in east, south and west areas of Iran. Despite the increase of the infection prevalence in Iran during 2000-2014, the highest incidence has been recorded during the years 2009- 2013 (7).

In the Eastern Mediterranean (EM) region, United Arab Emirates, Oman, Iraq, Saudi Arabia, Iran, Afghanistan, Pakistan and Palestine have reported the CCHF human cases. Iran and Pakistan annually report 50 or more cases of CCHF (8). Recently, high rate of CCHF was determined from *Hyalomma aegyptium* in Syria (9). Also, serological surveys among livestock diagnosed the disease in Egypt, Tunisia and Somalia. There was an unusual enhance in CCHF cases in Afghanistan with 237 reports across the country, mostly in Eid al-Adha (sacrifice feast in

Islam) (10).

According to a study by Palomar et al, in Spain in 2013-2015, they found that 1333 out of 2053 ticks were related to *Hyalomma marginatum*, 680 were belong to *H. lustanicum* and 40 were concern to *Rhipicephalus* ticks. All 2053 ticks were analyzed using PCR technique to search for the genome of the CCHF virus. On the other hand, 228 human serum samples that were regularly linked to ticks were tested for specific IgG antibodies against CCHF virus using indirect immunofluorescence Ab techniques. Eventually, no CCHF-infected ticks were reported. Likewise, no antibodies against CCHF virus were found in serum samples (11).

A study acheived by Panayotova et al, in 2016, for investigation of distribution of the CCHF virus and its potential risk to humans in ticks of the five regions in Bulgaria, where the CCHF virus had been reported in these areas for the last five years, viruses isolated from these ticks were classified into Europe 1 categories (the pathogenic species of the CCHF) and Europe 2 viruses (AP_92 and similar species AP_92). Europe1 CCHF virus was reported in 39 cases (6.3%) of 623 *H. marginatum*, while the Europe 2 CCHF virus was observed in 49 cases (11.8%) of 415 *R. sanguineus sensu lato* ticks. According to the study, both Europe1 and Europe2 virus strains of the CCHF virus were in Bulgaria (12).

Papa et al., in 2017 in Albany, studied the CCHF virus strains in relation to their geographical distribution. In 2007-2014, 726 ticks collected from lambs in the, 366 ticks were related to the species of *H. marginatum*, 349 ticks belonged to the *Rhipicephalus bursa* species and 11 ticks related to *Rhipicephalus sanguineus*. The Europe1 CCHF virus identified in the *H. marginatum* tick was collected from Albania's endemic areas, while the Europe 2 CCHF virus identified in the *Rhipicephalus bursa* ticks was found in different parts of Albania. The genetic category of both groups was reported in the endemic region of the CCHF virus, while only Europe 2 was detected in the south of Albany (13).

Risk factors

There are many individual groups considered to be at-risk of CCHFV infection, such as those who work with large domestic animals, and those caring for CCHF patients (nosocomial infection in health-care workers) which can be extremely high, particularly during the hemorrhagic period of infection (6). Although CCHFV has been isolated from numerous species of ticks, those of the *Hyalomma* genus are considered the primary vector in CCHF enzootic and endemic areas. The distribution of CCHFV is related to the *Hyalomma* ticks spread, hence, in areas lacking these ticks, the risk of taking infection is negligible. Crushing infected ticks and butchering infected animals are also crucial routes of CCHFV infection transmission (14). Humans become infected

with CCHF virus either through bites of infected ticks, which maintain a life-long infection and are competent reservoirs, or by

direct contact with virus contaminated tissues or blood. In addition to zoonotic transmission, CCHF virus can spread from person to person, though being among rare hemorrhagic fever viruses able to cause nosocomial outbreaks in hospitals with high standards of hygiene (15, 16).

Pathogenesis

The virus replicates in endothelial cells, macrophages and monocytes, leading to viremia status. Sometimes it can cause infection of target organs, such as brain, endothelial cells and the liver. The pathogenicity of the virus has not been well known. It has been hypothesized that the infection is caused by direct damage of the infected tissues and at the same time the indirect effect of the virus on the host's immune response, such as cytokines. There is a vital role exerted by inflammatory cytokines like IL-1, IL-6, TNF-α and IL-10 in the development of infection symptoms (17), It is more likely that the infection is mediated indirectly by increased levels of proinflammatory cytokines, or by a combination of virus infection and the cytokine storm (24, 25).

Also CCHFV employs a range of passive and active mechanisms to avoid induction of the antiviral type I interferon (18, 19).

The infection has a four-stage course, including a latent period, pre-hemorrhagic, hemorrhagic and a recovery phases. The incubation period depends on the route of infection, which varies from 1-3 days and may reach 9 days after tick bites. Clinical symptoms include fever, chills, muscle aches and pains. After 3-6 days, there is a hemorrhage that occurs mainly in the areas of mucous membranes and skin (especially in the upper body part). Internal hemorrhage leads to shock, pulmonary edema, and death. The mortality rate is 30-50% (28, 29).

Diagnosis

Early diagnosis of CCHF is essential in order to maintain patient's life and prevent infection spread. Infection with the CCHF virus can be unraveled by various laboratory tests including antigen-related antibody testing, antigen detection, serum neutralization, quantitative real-time polymerase chain reaction (RT-qPCR), and virus isolation. Immunological methods lack sufficient sensitivity in the first week of the infection toward detection of CCHF infection, while molecular methods such as RT-qPCR technique is considered an accurate and valid approaches (in terms of rapidity, sensitivity and specificity) for the CCHF virus identification (30, 31)

Treatment

Therapeutic measures should be taken immediately after diagnosis of the infection. Most patients with CCHF only receive supportive care which involves adjusting water and electrolyte balance and treating dysuria. Ribavirin oral administration is recommended in cases of suspected CCHF. The mechanism of this drug is not known exactly, but it is supposed that it modifies the nucleotide sequences and inhibits the transcription of mRNA in virus (5, 32 , 33). Additionally, favipiravir has been evaluated against CCHFV in vivo. This compound has been

confirmed as an efficient antiviral drug for the elimination of acute CCHF, through suppressing viral replication following CCHFV infection, even when treatment started 48 hours post-infection (PI) (20, 21).

Control measures

The main measure to control the infection is to avoid or reduce exposure to the virus. This can be performed by many ways. Individuals at high-risk works (i.e. veterinarians, slaughterhouse workers, Shepherds, campers, agricultural workers, sheep herders) must take preventive cautions to avoid exposure to virus infected ticks or virus-contaminated animal blood or other tissues. For instance, use gloves and restricted exposure of naked skin to fresh blood and other tissues of animals are proper preventive implementations (3, 22). Similarly, medical staffs in contact with CCHF suspected patients should follow standard barrier-nursing methods. Acaricide treatment of livestock in CCHFV endemic areas is important in decreasing the population of infected ticks.

CCHF cases occurring as an expected event in endemic areas should be notified to clinicians in the international neighborhood. Awareness must be taken of the probability of importation of CCHF cases from endemic areas, of human-to-human transmission, particularly in the nosocomial setting, and of the potential transmission of the virus via tick-infested and infected imported livestock (23). The preferred procedure to prevent the infection is to use personal tools, prevent vector's bites and limit contact with animals. There are currently no valid vaccines to prevent

human and animal infections, but in case of a person rapid therapy, the infection will be eliminated.

The CDC supervises timely referral of CCHF probable cases` sera to the National Reference Lab and provides immediate and free of charge treatment of patients. The Iranian Veterinary Organization collects suspected livestock` sera and ticks from high risk regions and sends the samples to the National Reference Lab. With prevention planning and control program for tick populations, the mortality rate of 20% (year 2000) was dramatically decreased to 6% in 2007. It is worth pointing out that the National Reference Lab, in addition to CCHF detection, has been well equipped with several serological and molecular assays for diagnosis and research on a wide variety of arboviruses and viral hemorrhagic fevers such as West Nile, Rift Valley Fever, Chikungunia, Hanta, Pumala, Dengue, and Yellow Fever (24). Increasing general awareness, application of pesticides (acaricides) and accomplishment of standard infection control precautions by health care staff is also essential for the decrease of CCHF risk (10).

Q fever

Q fever is a challenging infection as significant further investigations are necessary toward exact disclosure.

Great research opportunities are available to reach a better understanding and hence a better prevention and control of the infection. The disease spread through inhaling infected aerosol contaminated with placenta, birth fluids or urine and feces of infected animal even when dried (25). Q fever is also a zoonotic infection between humans and animals which is caused by an obligate intracellular bacterium *Coxiella burnetii* (*C. burnetti*) (26), which is a tick-borne (vectors), pleomorphic, gram-negative coccobacilli. The bacterium is morphologically very similar to *Rickettsia* spp, though the *C. burnetii* remains limited known agent. Bacterial intracellular and environmental persistence and infectious properties have been scarcely investigated. Further understanding of the interactions between the infected host and the bacteria is necessary. Owing to wide spread and low infectious dose, following the preventive strategies and surveillance is essential, though further research investigations are essential to clarify the Q fever epidemiology and provide better prevention strategies.

Causal agent

This bacterium can be transmitted via ticks (*Dermacentor andersonii*), urine, feces, milk, placenta, and amniotic fluid of animals. However, when these products become dry, the bacteria persists inactive for a long time and can spread as part of the peripheral dust in the air. *C. burnetii* is resistant to environmental stresses such as high temperatures, osmotic pressure and ultraviolet light (26). This bacterium is capable of changing the phase as passes two antigenic stages. Small cell varieties (SCVs) forms are resistant to heat, pressure, and mechanical agents, and survive well in the environment. Additionally, large cellular varieties (LCVs) proliferate only in host monocytes or macrophages (27). *C. burnetii* delays the phagosomes-lysosome fusion after penetrating the host phagosomes and is likely to convert from SCV to LCV mode through this mechanism. SCVs and LCVs can be distinguished using electron microscope (26). Owing to intracellular habitat, the bacterium does not proliferate *in vitro* conditions and is directly derived from patients or animals being in phase I of the infection. To isolate the bacterium, multiple passages through embryonic eggs or chicken embryos (in Phase II) should be carried out at 35°C and the maximum growth and development rate is close to the fetal death time. The time for bacterial isolation in chicken embryo is approximately 12 hours. Tissue culture is also possible using endothelial cells or embryonic fibroblasts of chickens or mouse cells. The bacterium in Phase I of the infection with a capsular polysaccharide and a high pathogenicity is isolated from patients or infected animals, which is used for production of the vaccine. Bacteria in phase II are less pathogenic and lose the capsule due to frequent growth in embryonic eggs.

Epidemiological studies in Iran

Doosti et al, in 2012, used PCR techniques to examine the presence of DNA in the blood of 130 camels. Of these, 14 samples were reported

positive for *C. burnetii*. In a study by Kargar et al, in 2013, 100 samples of cow's milk were examined for the presence of *C. burnetii*, of which 11% were positive. Khalili et al, 2009 measured the titer of anti-phase II antibodies in slaughterhouse animals, with 68% of them reported IgG positive (28).

Ezatkhah et al., in 2015 reported that 33.9% of sheep and 22.4% of goats in the southern regions of Iran had antibodies to *C. burnetii* (29). In a study carried out by Esmaeili et al. in 2016, 190 samples of the serum were tested by ELISA test, from which 14.4% were reported to be positive for *C. burnetii* (44) In a study by Rizzo et al in Italy 2016, 5738 sheep and goat sera were collected and analyzed using ELISA test for the presence of specific IgG antibodies to *C. burnetii*, they found that 15.9% of the samples were positive for specific antibodies(45). In a study on epidemic of *C. burnetii* was carried out by Bond et al, 2016 in Australia. They found that prevalence of *C. burnetii* in non-pregnant goats was 15%, and the morbidity of the infection was 49.5% as evaluated by PCR technique (30) . Alves et al in Portugal 2017, recorded seven patients with hepatitis, and evaluated the epidemiologic history of Q fever. Identification of Q fever agent was performed in 5 cases using PCR test, and the results were positive for both serologic and genetic tests (PCR) (serologic tests were negative at the beginning of the infection)(47). Gache et al, in France observed that 36% of cows, 55% of sheep and 61% of goats were positive for Q fever. In addition, the abortion rate associated with *C. burnetii* in 2695 cattle, 658 sheep and 105 goats were examined using PCR techniques (48). In a study carried out by Van Roeden et al in 2018, 439 febrile people were examined. In 166 cases, chronic fever has been reported, with 14% acute aneurysm, 13% of heart problems and 10% of non-cardiac abscesses. The mortality rate for acute febrile seizures was 38% (49, 50). This bacterium can also infects pets, such as dogs, cats, and rabbits(51).

Pathogenesis

The infectious dose (ID_{50}) of this organism is responsible for the pathogenicity of inhaled bacteria through respiration. The low pathogenicity dose of *C. burnetii* (1-10 CFU/ml) has made this bacterium one of the most pathogenic organisms around the world (52). Q fever is appeared in two forms, acute and chronic forms, but noticeably asymptomatic condition is very common. The Q-fever has various clinical symptoms and the symptoms of each area changes to other areas (53). Since the infection has variable and non-specific symptoms and the fever does not always occur, it is usually difficult to diagnose the infection. The mortality rate is 1-2%. Endocarditis is one of the main causes of death, occurs in 1% of cases.

The most important route of infection is inhalation of bacteria-contaminated dust, while the oral route is considered of secondary importance. Once inhaled or ingested, the extracellular form of *Coxiella burnetii* (or SCV after small-cell variant) attaches itself to a cell membrane and is internalized into the host cells.

Phagolysosomes are formed after the fusion of phagosomes with cellular acidic lysosomes.

The multiple intracellular phagolysosomes eventually fuse together leading to the formation of a large unique vacuole. *Coxiella burnetii* has adapted to the phagolysosomes of eukaryotic cells and is capable of multiplying in the acidic vacuoles [50]. In fact, acidity is necessary for its metabolism, including nutrients assimilation and synthesis of nucleic acids and amino acids. Multiplication of *Coxiella burnetii* can be stopped by raising the phagolysosomal pH using lysosomotropic agents such as chloroquine.

Mo, Akporiaye and Baca identified three proteins involved in intracellular survival: a superoxide dismutase, a catalase, and a macrophage infectivity potentiator (Cbmip). *In vitro* studies on persistently infected cells with phase I and phase II bacteria reported a similar mitotic rate in infected and noninfected cells (23). Moreover, the authors frequently observed asymmetric cellular divisions in infected cells and suggested that this phenomenon could allow maintenance of persistent infection.

The intracellular cycle of *Coxiella burnetii* leads to the formation of two development stages of the bacterium known as "small-cell variant" (SCV) and "large-cell variant" (LCV).

LCVs can differentiate into spore-like bacteria by binary asymmetrical division. The endogenous spore-like forms can undergo further development and metabolic changes until finally reaching the SCV form. Finally, cell lysis, or possibly exocytosis, releases the resistant bacteria into the extracellular media.

Infection forms

The acute form of the infection is similar to the flu with some degree of pneumonia and hepatitis. Symptoms may occur 3 to 30 days after exposure to the bacteria in this form, which include fever, severe headache often exacerbating the eyes, sweating, muscle aches, joint pain, loss of appetite, fatigue, and severe weight loss. Skin rashes occur in 5-20% of cases. Hepatobiliary is associated with jaundice in rare cases, but hepatomegaly enlargement and elevated levels of liver enzymes are common. The acute form of the infection is usually self-limited and in some cases causes death (31 ,26). In people with underlying illnesses, heart valve impair, blood vessel abnormalities, immune deficiency and acute renal failure, the acute form of the infection can be fatal. In chronic condition, usually there is no fever. The chronic condition of the infection can develop a month or even one year after the acute form of the infection. Due to the delay between the development of the infection and its diagnosis at this stage, the mortality rate increases in chronic form. The most common chronic symptoms include endocarditis and osteomyelitis appeared usually in patients with underlying illness. Chronic fatigue syndrome and cardiovascular infection are the long-term complications of this phase of the infection (32). Patients with negative culture of endocarditis

should be considered as positive-Q fever. Without antibiotic therapy, endocarditis is usually fatal (Parker et al., 2006).

Most articles published in the context of Q fever in children are case reports. Because the fever is usually not diagnosed in children, the general belief is that fever is rare among children. Clinical manifestations of Q-fever in children are similar to those in adults, and fever is self-limited, but in rare cases, it may be associated with death. Osteomyelitis and endocarditis occur in chronic conditions, and fever can recur again. Fever has been reported in all countries except New Zealand, and the last epidemic were in the Netherlands in 2008, where a 2,300 people affected by fever.

Symptoms of the infection are non-specific and are not helpful in the diagnosis. An examination of the history of contact with cattle, sheep and goats can be helpful. Children suspected to have a fever should be checked for heart valve infection because they may be predisposed to endocarditis.

Diagnostic approaches

Methods for diagnosis of Q fever include:

1) Serology: Indirect immunofluorescence (IF) is a reference method for serological diagnosis. Enzyme immunoassay (EIA) and complement fixation (CF) are routine methods used in serology. The CF test is more long-lasting and has less specificity than the IF test. Serological diagnostic tests for Q-fever have cross-reactivity with *Legionella* and *Leptospira* spp infections (33, 34). Khalili et al, in 2010, used ELISA to test the phase I antibodies in patients with suspected Q fever in Iran, and 24% of patients had the phase I antibodies and 36% had phase II antibodies.

2) PCR technique: If the PCR test gives positive result before antibodies detection, it can be used as a rapid diagnostic method. The PCR test is highly valid and accurate in tissue samples taken from the heart valves because of large number of bacteria (35, 36)

3) Histology and other laboratory methods: Histological findings are mostly non-specific. Immunostaining is beneficial for fresh tissue samples and those that have been fixed using formalin (40, 53, 58) In the acute phase of the infection, the count of white blood cells is usually normal; thrombocytopenia is observed in 25% of cases with increased in the level of liver enzymes (59).

Treatment and control

The drug of choice for the Q-fever eradication includes doxycycline. The duration of drug consumption varies, depending on the type of illness (acute or chronic). In chronic condition, doxycycline is used for a period of 18 months to several years (to prevent the infection recurrence). In case of endocarditis, doxycycline consumption should be accompanied by quinolone for 2 to 4. It is notable that even in the acute form of the infection, there is possibility of healing of untreated patient, and in case of incomplete healing, the patients should receive doxycycline for 2-3 weeks. Even after complete treatment, its

necessary to follow-up the case.

In the case of a Q fever outbreak, sanitary and prophylactic measures should be applied at herd and human level, in order to limit infection transmission. Human and animal infections must be diagnosed early and treated immediately to prevent the development of chronic infections and secondary complications.

In France, when Q fever has been diagnosed in a herd on a cheese-producing farm, milk of the aborted females must be discarded. Indeed, sale, transformation, and treatment of this milk are strictly forbidden.

In the UK, Health Protection Agency guidelines suggest the use of 2% formaldehyde, 1% Lysol, 5% hydrogen peroxide, 70% ethanol, or 5% chloroform for decontamination of surfaces, and spills of contaminated material should be dealt with immediately using hypochlorite, 5% peroxide, or phenol-based solutions (34, 37, 38).

Prevention of direct contact with amniotic fluid and animal secretions, vaccination of livestock, and the application of quarantine rules for imported livestock are necessary measures of prevention of infection(62) In Cyprus, the prevalence of Q fever among sheep and goats was reduced by destroying infected aborted material, isolating infected dams and disinfecting the premises.

Vaccination with inactive whole-cell bacteria has been performed and proved effective in humans and animals. However, inactive whole-cell vaccines present several defects. Recombinant vaccines have been developed in experimental conditions and have great potential for the future (34).

Live and cellular vaccines for the infection are being studied and some of them have been approved. A full-cellular vaccine has been licensed in Australia (Q-Vax) and also vaccines produced from bacterial residues and deactivated using phenol-chloroform (CMR) have been approved in the United States (63).

Conclusion

The rate of CCHF and Q fever as zoonotic infections has remained high in most of regions worldwide. Hence implementation of accurate control strategies can help prevent its spread. Use of ticks' repellants, control of livestock and wildlife movements and multinational policies are also essential in this regard. Noticeably, it is necessary to establish and empower the international surveillance fulfills to better predict, investigate and control these infectious diseases, improve the international public health infrastructure, develop enhanced international guidelines,

and recommendations to improve the international capabilities toward restriction of disease outbreaks with adequate medical and scientific resources and expertise. To predict and monitor the CCHF and Q fever, regional rather than countrywide scale cooperation is necessary. Immigration/travel also remains an important factor influencing the spread of these agents.

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Conflict of interest

None

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