Journal of the Egyptian Society of Parasitology, Vol. 53, No.1, April 2023
J. Egypt. Soc. Parasitol. (JESP), 53(1), 2023: 35 – 50
Online: 2090-2549

ZOONOTIC BARTONELLOSIS: IS IT THRERATING TO THE EASTERN MEDITERRANEAN COUNTRIES?

By
TOSSON A. MORSY[1], SARYA MOHAMED HAWAM[2], HAITHAM A. El HADIDY[3] and SHERIF AHMED MEGAHED AHMED[4]
[1]Department of Parasitology, Faculty of Medicine, [2]Department of Microbiology, Military Medical Academy, Cairo, 11291 and [3]Hospital Administration, School of Medicine, Badr University, [4]Department of Internal Medicine, Faculty of Medicine, Ain Shams University, Cairo, 11566[1,4], Egypt (Correspondence: [1]tossonmorsy@med.asu.edu.eg or morsyegypt 2014@gmail.com, Orcid.org/0000-0003-2799 2049; [2]saryahawam@yahoo.co.uk; [3]haitham.elhadidy63@gmail.com; [4]sherifmegahed@med.asu.edh.eg)

Abstract

Bartonellosis is a group of emerging and re-emerging bacteria of *Bartonella* genus with world-wide distribution. *Bartonella* species cause diseases such as Carrión's disease, trench fever, cat scratch disease, bacillary angiomatosis, peliosis hepatis, chronic bacteremia, endocarditis, chronic lymphadenopathy, and neurological disorders. Fleas, lice, sand-flies, bed bugs, ticks, mites, and even spiders transmit infection to man, domestic and wild animals. Infection is establishing intracellular replication niches and subverts diverse pathways of host's immune system. Bartonellosis can subclinical bacteremia to broad spectrum of clinical symptoms in man ranged from a mild flu-like intermittent fever to more severe manifestations such as, arthralgia, arthritis, endocarditis, hepatitis, myocarditis, neuroretinitis, uveitis, vasoproliferative tumors and even death.

Effective antibiotics include rifampin, ciprofloxacin, gentamicin, and trimethoprim/sulfamethoxazole. But, *B. henselae* is generally resistant to penicillin, amoxicillin, and nafcillin. Doxycycline and rifampin in combination are recommended to treat neuroretinitis. Treatment must be adapted to each clinical situation, species, and acute or chronic disease, but in a timely manner.

Key words: Bartonellosis, Man, Animals, Vectors, Pathogenesis, Diagnosis, Treatment

Introduction

Bartonella species are fastidious, gram-negative bacteria, which cause a wide manifestations range including the cat scratch disease (CSD), bacillary angiomatosis (BA) and other infections in patients with HIV infection, as well as the endocarditis (Raoult *et al,* 1996). *Bartonella* has emerged as one of the leading causes of the culture-negative endoarditis (Spach *et al,* 1995). *Bartonella* was very difficult to be isolated and characterized. Bartonellosis was reported in Peru since the pre-Columbian cultures age (Perez and Ogusuko, 1995). But, some publications contained incomplete information as to treatment or historical aspects (Neves *et al*, 2003). Analysis of *Bartonella* 16S ribosomal RNA identified and classified this species (Spach and Koehler, 1998). Bartonellosis caused by *Bartonella* spp emerged as zoonoses of vector borne diseases (VBD) complex (Chomel and Kasten, 2010). Many *Bartonella* species are pathogenic to people, any of which is referred to broadly as bartonellosis, although some infection forms have common names such as cat scratch disease (CDC, 2022).

Review and General Discussion

Bartonella spp. belong to the alpha-2 subgroup of the Proteobacteria based upon 16S ribosomal RNA testing and are closely related to the genera *Brucella* and *Agrobacter ium*. Prior to 1993, the only member of the *Bartonella* genus identified was *B. bacilliformis*. DNA hybridization outcome (Brenner *et al,* 1993) led them to propose that the genera *Grahamella* and *Bartonella* must be unified and that the latter name must be retained. Brenner *et al.* (1995) by *Grahamella* species taxonomic analysis completely studied all members of family Bartonellaceae, which supported the proposal that this family must be out of order Rickettsiales. Roux and Raoult (1995) reported that the species of the genus *Rochalimaea*, recently renamed

Bartonella, are of a growing medical interest. They concluded that the restriction fragment length polymorphism after PCR amplification of the 16S-23S rRNA Gene ITS was useful for rapid *Bartonella* species identification, and PFGE could be an efficient mean for isolate identification.

Microbiology: *Bartonella* is gram-negative, pleomorphic bacteria very poorly stain in tissues using Gram stain but will stain black with silver-impregnated stains, such as Warthin-Starry stain. Routine culture procedures have low yield, unless the cultures are held for an extended period. *Bartonella* spp growth is optimized when specimens are incubated in fresh media at 35 to 37ºC with 5 to 10% CO_2 and more than 40% humidity; but *B. bacilliformis* grew better at 25 to 30ºC. Best medium is freshly prepared rabbit-heart infusion agar also grow on various forms of chocolate or blood agar (Welch *et al,* 1993)

Bartonella typically does not trigger automated CO_2 detection systems. *Bartonella* was identified by using acridine orange staining of blood culture broth after seven days of incubation (Larson *et al,* 1994). Chemical defined, cell-free, extract-free, liquid medium helped *Bartonella* spp growth including clinical specimens (Wong *et al,* 1995). A chemical-modified used insect-based liquid culture medium allowed growth of at least seven *Bartonella* species, including *B. henselae* and *B. quintana* (Maggi *et al,* 2005). Growth of *Bartonella* from biopsy specimen successded by using tissue homogenates cocultivated with endothelial cell monolayers, but microbiology laboratories don't routinely do these techniques (Koehler *et al,* 1992).

Signs and symptoms: *Bartonella* infections caused a broad clinical spectrum ranging from asymptomatic self-limited infections to severe disease with high morbidity and mortality rates, with etiologic agents of culture-negative infective endocarditis varied from 0.1% to 4.65% of all endocarditis cases (Chaloner *et al,* 2013), symptoms wide range included fever, hepatitis lymphadenitis endoc arditis, and myocarditis (Buffet *et al,* 2013).

Of more than 33 *Bartonella* proved species, majority were hosted by rodents (Szewczyk *et al*, 2021). The commonest species cau se human disease are *B. bacilliformis, B. quintana,* and *B. henselae*; others also caused human diseases (Daly *et al,* 1993), but without well defined role were *B. grahamii* (Birtles *et al,* 1995), *B. tribocorum* (Heller *et al,* 1998), *B. clarridgeiae* (Margileth and Baehren, 1998), *B. vinsonii* (Roux *et al,* 2000), *B. washoensis* (Kosoy *et al,* 2003), *B. koehlerae* (Avidor *et al,* 2004), *B. alsatica* (Raoult *et al,* 2006), *B. rochalimae* (Eremeeva *et al,* 2007), *B. rochalimae* (Lin *et al,* 2008), and *B. tamiae* (Kosoy *et al,* 2008). Certain *Bartonella* species cause a febrile bacteremia in man and animals, including *B. quintana*, agent of trench fever, and *B. henselae* agent of cat-scratch disease (Vayssier-Taussat *et al,* 2016). *B. elizabethae* infection may be more common than previously known; serologic samples collected in 1997 & 1998 from 204 injection drug users in New York showed 46% were *B. elizabethae* positive (Comer *et al,* 2001). Also, using 16S RNA gene sequencing identified a serogroup of *B. henselae* "*marseille*" (Drancourt *et al,* 1996). The 16S ribosomal DNA analysis was used to differentiate *Bartonella* spp, which nucleotide base sequence data for a 940-bp fragment of citrate synthase-encoding gene (gltA) was more valid than 16S ribosomal DNA sequence data for the evolutionary relationships of *Bartonella* spp. (Birtles and Raoult, 1996). Phylogenetic studies determined that most virulent *B. bacilliformis* is only representative of an ancestral lineage, and others that cause human disease have evolved in a separate lineage; the evolution of newer species correlated with their adaptation to distinct mammalian reservoirs (Saenz *et al,* 2007).

Transmission: Numerous mammalian species, including wild animals such as rodents and domestic such as dogs, cats, and man act as reservoir hosts for many *Bartonella* species, vectors transmitted bacteria and pets' and their ecto-parasites pose a serious risky zoonosis (Iannino *et al,* 2018). *Bartonella*

spp. survives in different hosts and reservoirs for months to years as an opportunistic pathogen (Portillo *et al,* 2020). VBDs are human illnesses caused by parasites, viruses, and bacteria usually transmitted by a blood-sucking arthropod amounted to 27% of all world infectious diseases in Tropics & subtropics (WHO, 2018). But, climatic changes and globalization have exposed much more people in other parts of the world to risk of acquiring VBDs (Morsy *et al,* 2022).

Reservoirs: Most *Bartonella* spp. causing human disease is associated with well-known mammalian reservoirs, including man himself, domestic animals, and wild animals, which may have prolonged *Bartonella* spp infection (Breitschwerdt and Kordick, 2000)

Cats: Epidemiologic data incriminated that cats are the main reservoir for human *B. henselae* infection (Koehler *et al,* 1994). In California, *B. henselae* was reported in 56% of cats less than a year of age, 34% of those at least one year of age and 77% one year or older (Chomel *et al,* 1995). *Bartonella* bacteremia was more common in pet cats by CSD patients compared to control cats 89% versus 7/25 (Kordick *et al,* 1995). Role of cat contacts as source of human infection reported 4/5 *B. henselae* isolates from human owners (Chang *et al,* 2002). Cats infrequently display clinical signs of *B. henselae* infection, even with persistent infection (Dehio, 2008). By autopsy, they showed abnormal histopathology; peripheral lymph node hyperplasia, splenic follicular hyperplasia, lymphocytic cholangitis/pericholangitis, lymphocytic hepatitis, lymphoplasmacytic myocarditis, and interstitial lymphocytic nephritis (Kordick *et al,* 1999). There may be strain differences in ability to cause overt infection in cats. Among nine cats inoculated with *B. henselae* virulent strain of (LSU16), all developed an inoculation papule, a febrile illness, and bacteremia by day 14, with a peak at 14 to 28 days post-infection, with strong antibody responses determined by ELISA (O'Reilly *et al,* 1999).

In France, *B. clarridgeiae* was detected in the blood of 15/94(16%) stray cats (Heller *et al,* 1997). In San Francisco, two new *Bartonella* species; *B. koehlerae* were characterized from 25 isolates recovered from the cats (Droz *et al,* 1999).

Bats: Morse *et al.* (2012) in USA detected bartonellae in some female bat flies and their pupae suggested vertical transmission across developmental stages. They added that bartonellae specific function in bats and bat flies was a debate subject. Judson *et al.* (2015) in USA that reported that high prevalence and sharing of bartonellae in bat flies and bats supported a role of bat flies as a potential vector for *Bartonella*, suggesting that bartonellae could spill over into humans and animals sharing the landscape. Corduneanu *et al.* (2018) in Romania detected the first *Bartonella* spp. DNA in bats' heart tissues from central and Eastern Europe. By phylogenetic analysis identified four new *Bartonella* spp. sequences closely related to bats' species isolated in Europe and North America.

Humans: Multiple lines of evidence suggest that humans are the primary reservoir for *B. quintana* and *B. bacilliformis* (Rolain *et al,* 2004). Both of these organisms can establish prolonged infection in humans, and invasion and persistent infection of red blood cells play a major role in *Bartonella* establishing chronic human infections. Also, organisms persist in red blood cells enables transmission via blood-sucking arthropods (Greub and Raoult, 2002).

Other species were *Candidates B. mayotimonensis* and *B. melophagi* isolated from aortic valve in-patient with culture negative endocarditis and in patients' blood with consistent bartonellosis symptoms (Maggi *et al,* 2009). Bats species that cause human disease are *B. vinsoni* subsp. *berkhoffii*, *B. claridgeiae, B. tamiae, B. rochalimae, B. elisabetae, B. koehlerae, B. graham* and *B. balsatica* (Diaz *et al,* 2012). Lin *et al.* (2010) reported that CSD in patients necessary to diagnose with adenopathy, to differentiate CSD to some neoplastic diseases, such as lymphoma, leukemia, and other neoplasms and la-

rge specter of emerging infectious diseases, as fungal infection, toxoplasmosis, tularemia, tuberculosis, plaque, lymphogranuloma venerum (LGV), AIDS, and syphilis.

Candidate's B. ancashi was isolated from a patient's blood with *Verruga peruana* in Peru (Mulinsk *et al,* 2013). *B. hensellae, B. quintana*, and *B. bacilliformis* were isolated from patients (mainly children) in wide array of clinical syndromes (Bass *et al,* 1997).

Rats, mice and dogs: In an extensive analysis of rats from 13 sites in the United States and Portugal, *Bartonella* spp were isolated from the blood of 19% *Rattus norvegicus*, and 112% *Rattus rattus* (Ellis *et al,* 1999). The analysis of the *Bartonella* spp isolated from these rats showed they were most similar to *B. elizabethae. B. elizabethae* has also been isolated from a rat in Peru (Birtles *et al,* 1999). *B. vinsonii* appears to have both mice and dogs as reservoirs (Breitschwerdt *et al,* 1998). These pathogens, however, do not play a major role in human disease.

Vectors: So many different vectors transmit *Bartonella* species, which include fleas, lice, and sand flies and potentially ticks, mites, spiders and even contaminated shoes.

Fleas: The cat flea, *Ctenocephalides felis*, serves as the major vector for cat-to-cat *B. henselae* transmission. Some flea-to-human transmission may occur, but evidence suggested human infection occurred predominantly with cat contact, from a scratch, lick, or bite (Margileth, 2000).

Lice: *Bartonella*-like bacteria were recovered from four of nine small rodents, but none of strains was classified as *B. bacilliformis* by serologic and genotypic methods. Five of these isolates may represent three previously unrecognized *Bartonella* spp, and one was a strain like *B. elizabethae* (Raoult and Roux, 1999). Human-to-human transmission of *B. quintana* occurs via contact with human body or head lice *Pediculus humanus corporis* or *P. h. capitis* (Bonilla *et al,* 2009), specifically as a result of cutaneous inoculation of lice feces on skin by scratching, identified *B. quintana* from homeless persons' lice (Foucault *et al,* 2006). Angelakis *et al.* (2011a) in Ethiopia isolated *B. quintana* from rural populations. Angelakis *et al.* (2011b) in France reported that head lice nits were positive by real-time PCR, and intergenic spacer region gene sequences completely agreed with ITS fragment of *B. quintana* genome determined head louse role in transmissioin. Trape and Raoult (2012) in Senegal recovered *B. quintana* from females one of whom suffered from endocarditis. Diatta *et al.* (2014) in rural Senegal detected *B. quintana* in feverish patients and her head lice.

Sandflies: The *Lutzomyia* (New World) & *Phlebotomus* (Old World) sand-fly has clearly been identified the *B. bacilliformis* vector. In South America, bartonellosis, or Carrion's disease has been described as an exotic disease (Maguiña *et al,* 2001). Lozano-Sardaneta *et al.* (2019) in Brazil detected *Bartonella* sp. in sandflies outside an endemic area of Verruga Peruana.

Bed bugs: *Cimex lectularius* and *C. hemipterus* adults and immature stages can acquire and maintain for > 2 weeks and release in feces viable *B. quintana* organisms after a stercorarial shedding, with progeny vertical transmission (Leulmi *et al,* 2015). Bed bugs contained neutralizing factors that attenuate pathogen virulence and decrease their ability to transmit infection (Lai *et al,* 2016). El Hamzaoui *et al.* (2019) suggested that bed bugs might be competent vectors of *B. recurrentis*, as bed bugs and body lice share the same ecological niches

Ticks: Kim *et al.* (2005) in Korea reported bartonellosis in 6.7% *Apodemus agrarius* (striped field mouse) and 11.1% in *Eothenomys regulus* (Korean red-backed vole) and 12.1% in an insectivore, *Crocidura lasiura*. The *Bartonella* DNA was in *Haemaphysalis longicornis, H. flava* and *Ixodes nipponens is*, and that ticks were added to *Bartonella* vectors list. Telford and Wormser (2010) in USA reported that although some reports suggested possible tick transmission of *Bartonella* species, a critical review of this issue concluded that *Bartonella* transmitted by

ticks was not well established. Sytykiewicz *et al.* (2012) in Poland reported the occurence of *B. henselae* and *Borrelia burgdorferi* sensu lato in *Ixodes ricinus* collected from the central and eastern parts, but presence spirochetes was ascertained in both nymphal and adult ticks. Kamani *et al*. (2013) in Nigeria tick-borne pathogens are recognized as important aetiological agents of human and animal diseases Müller *et al.* (2016) in Austria reported IgG antibodies against *Bartonella* species in sera from hunters (100) and blood donors (100): in hunters 23% were positive for *B. quintana* and in 2%, antibodies to *B. quintana* & *B. henselae*; in blood donors 22% were *B. quintana* positive, 1% for *B. henselae* & 5% for both. They concluded that exposure to ticks didn't constitutes a relevant risk for *Bartonella* infection.

Pathogenesis: Pathogenesis of *Bartonella* infection in humans is not well understood. But, *Bartonella* species are responsible for emerging and re-emerging diseases worldwide (Angelakis and Raoult, 2014). Bartonellae subvert multiple cellular functions of human endothelial cells, resulted in cell invasion, proinflammatory activation, suppression of apoptosis, and stimulation of proliferation that can cumulate in the vasoproliferative tumor growth (Anderson, 2001). *Bartonella* species caused human infective endocarditis are *B. quintana, B. henselae, B. elizabethae, B. vinsonii, B. koehlerae,* and *B. alsatica,* but more than 90% of these involved either *B. quintana* or *B. henselae* (Okaro *et al,* 2017). The co-infection *B. hensellae* and HIV, among numerous multisystem changes, developed tumor lesions on the face, like Kaposi sarcoma, and in the purple dermal nodes sites of thoracic and abdominal region, the histological verified as vasculitis accompanying by large specter of opportunistic agents (Podsiadly *et al,* 2003). *Bartonella* endocarditis clinical picture is similar to that of subacute bacterial endocarditis caused by others, with non-specific symptoms, such as fever, fatigue, and weight loss (Edouard *et al,* 2015). Cat scratch disease may cause parinaud oculoglandular syndrome, neuroretinitis, or retinochoroiditis focus (Cunningham and Koehler, 2000), retinal artery occlusion in patients with a permanent visual field defect (Eiger-Moscovich *et al,* 2016), and neuro-ocular manifestations (Jurj a *et al,* 2022).

In severely immunodeficient patients (pulmonary tuberculosis, carcinomatosis, HIV infection, patients undergone organ transplantation...etc.), *Bartonella* infections were difficult and often with unpredictable course of fatal prognosis (Andric *et al,* 2018). Lins *et al.* (2019) in Brazil reported that *B. bacilliformis, B. quintana,* and *B. henselae* gave symptoms; Peruvian wart by *B. bacilliformis*, indistinguishable from bacillary angiomatosis caused by other two species. Others include maculo-papular rash in trench fever, papules or nodules in cat scratch disease, and vasculitis associated with endocarditis, and febrile morbilliform rash, purpura, urticaria, erythema nodosum, erythema multiforme, erythema marginatus, granuloma annularis, leukocytoclastic vasculitis, granulomatous reactions, and angioproli-fer-ative reactions occur (Nawrocki *et al,* 2020)

Interaction with erythrocytes: Flagella play a major role in the organism's search for potential host cells and may also assist in binding to erythrocytes. Cell binding involves attachment to a red blood cell glycolipid receptor and the release of deformin, a compound that induces extensive indentations in erythrocyte membranes (Mernaugh and Ihler, 1992). Cell entry involved several processes, including flagellum-induced entry into the invaginations created by deforming and a not clear process elucidated that involves the invasion associated locus proteins A and B (known as IalA & IalB); these proteins were synthesized from the invasion-associated locus gene region known as ialAB (Minnick *et al,* 1996).

The *Bartonella* species enter the cell either free within the cytosol or within a vacuole, or subsequently replicate primarily in the erythrocytic vacuole. Eventually, the organism can escape from the cell and, in some insta-

nces, causes cell lysis; the cell lysis correla tes with the anemia frequently associated with clinical *B. bacilliformis* infection. Alcoholics may have more bacteria per erythrocyte than healthy blood donors (Rolain *et al,* 2003).

Interaction with endothelial cells: *B. quintana, B. henselae,* and *B. bacilliformis* all interact with endothelial cells and all induced angiogenesis. Three mechanisms were used to explain *Bartonella*-associated vascular proliferation (Riess *et al,* 2004): 1-Enhanced endothelial cell proliferation, 2- Inhibition of endothelial cells' apoptosis, & 3- Increased secretion of vasculoproliferative cytokines.

B. quintana adheres to endothelial cells, is engulfed by the cells, and appears within the cell as a cluster of organisms within a vacuole, similar to morulae formed by *Ehrlichiae* or *Chlamydiae* species. *B. quintana* appeared intracellular when patients' heart valves with *B. quintana* endocarditis by microscopy examined (Brouqui and Raoult, 1996).

B. bacilliformis produces an angiogenesis factor that is heat-sensitive, proteinaceous, and has a molecular weight of 12 to 14 kDa. *B. henselae* aggregates on the endothelial cells'surface engulfed and internalized in either *Bartonella*-contains vacuoles with one or small clusters of organisms or a unique host cellular structure, invasome with a large cluster of organisms (Eicher and Dehio, 2012).

B. henselae infection of endothelial cells *in-vitro* leads to activation of hypoxia-inducible factor-1 (HIF-1), key transcription factor involved in angiogenesis (Kempf *et al,* 2005). HIF-1 subsequently triggers the production of vascular endothelial growth factor (VEGF) leads to proliferation of endothelial cells. The stimulated cells, in turn, enhance the growth of *B. henselae* in a positive feedback loop (Kempf *et al,* 2001). Activation of HIF-1 depends on the expression of *Bartonella* adhesin A (formerly known as type IV pili), a very large protein that mediates binding of *B. henselae* to extracellular matrix proteins and to endothelial cells (Dehio *et al,* 1997).

cal vein cells and extracellular matrix protein, *B. henselae* induced longterm endothelial survival and angiogenesis (Kirby, 2004). The organism produced more angiogenesis than did treatment with VEGF itself. The results could explain how *B. henselae* causes vasoproliferative disorders, such as bacillary angiomatosis and peliosis hepatis. *B. henselae* development in HIV-infected individuals was traumatic associated with cats'contact (scratches or bites), and domestic cats (Regnery *et al,* 1995). *Bartonella* infections can cause serious morbidity and mortality in people HIV, especially those with advanced immunosuppression (Pape *et al,* 2005). *Bartonella* species increase the NF kappa-beta production by endothelial cells, a process recruiting monocytes and macrophages, thereby expanded bacterial cell habitat (Dehio, 2003).

Immune response: The immune response to *Bartonella* infections has become an active subject of investigation. The type and severity of the infection typically correlates with the host's immune function (Resto-Ruiz *et al,* 2003). One study of the immune response to *B. henselae* infections in immunocompetent mice found infection with this organism induced a cell-mediated immune response with a Th1 phenotype. In particular, after *B. henselae* was inoculated into the peritoneum of mice, the animals developed cellular proliferative responses, mainly from CD4 cells, that peaked eight weeks after infection (Arvand *et al,* 2001).

In response to the infection, animals increased production of interferon (IFN)-gamma, but not interleukin (IL)-4. Musso *et al,* (2001) in Italy found that *B. henselae* entered into macrophages within 30 minutes with peaked at 160 minutes, and that treating cells with IFN-gamma significantly decreased of intracellular *B. henselae* number and IFN-gamma was associated with nitric oxide release. They concluded that IFN-gamma activation of macrophages likely plays a major role in clearing *B. henselae* infection, and this microbial activity of IFN-gamma is me-

diated largely by nitric oxide production. Type IV secretion system proteins produced by *Bartonella* spp played a significant role in erythrocyte binding and in subversion of multiple host endothelial cell functions that are critical for establishing chronic infection (Foucault *et al,* 2002). In humans, increased IL-10 production among homeless persons with *Bartonella* bacteremia and IL-10 overproduction correlated with an attenuated inflammatory response with a marked role in persistent infection among them (Capo *et al,* 2003). The *B. quintana* lipopolysaccharide is a potent antagonist of Toll-like receptor 4 (Popa *et al,* 2007)

Diagnosis: Diagnosis of CSD must depend on a combination of epidemiological, histological, and bacteriological criteria, since no single criterion may be the gold standard. Laboratory diagnosis included serological tests (Western blot, ELISA, IFA tests, and PCR/DNA detecttion), culture, histopathology, and PCR.

Laboratory diagnosis of *Bartonella* infection generally includes serology, nucleic acid amp-lification testing (NAAT), and culture. However, blood smears microscopy for Carrión's disease (*B. bacilliformis*) using silver staining was neither highly specific nor differentiate species, or lymph node aspiration for diagnostic purposes (Versalovic *et al,* 2011).

Serology and protein-based tests: 1- IFAT for *B. henselae* antibodies in serum diagnose the acute cat scratch disease, and confirmed by PCR. But, IFA is limited by the antibody cross-reactivity with other bacteria species, and *Bartonella* spp. often evade an immune response and may give a false results and it may cause discrepancies between PCR and serology test results. IFAT for *Bartonella* infection diagnosis gave poor sensitivity (Vermeulen *et al,* 2007). 2- ELISA is another test, but with a low sensitivity (17-35%). 3- Western blot for detection of *Bartonella*-associated proteins was used, but lacks clear immunoreactive profiles. 4- PCR test from a single blood draw is not sufficiently sensitive for *B. henselae* with high false negative rates due to a small sample volume and levels below molecular detection limit (Duncan, 2007). Nowadays, real time ssrA PCR assay proved suitable for detection and identification of *Bartonella* species in human clinical specimens (Vesty *et al,* 2022).

Bartonella spp. are fastidious, slow-growing bacteria that are difficult to grow using traditional solid agar plate culture methods due to complex nutritional requirements and potentially a low number of circulating bacteria (Colson *et al,* 1996). Specialized culture techniques as Schneider's *Drosophila*-based powder medium or based on growth enrichment in modified media combined with the PCR assays and subculture bacterial isolation (BAPGM platfo-rm) developed to enhance *Bartonella* infection detection (Lynch *et al,* 2011). Validation of the BAPGM enrichment blood culture/PCR platform for the assessment of *Bartonella* spp. bloodstream infection in dogs was reported (Maggi *et al,* 2005). Thus, the BAPGM platform has been used diagnostically to assess bloodstream infection in dogs, other animals (Randell *et al*, 2018) and in humans (Rossi *et al,* 2015).

Differential diagnosis: Atypical mycobacterial diseases must be differentiate from: 1- Coccidioidomycosis and valley fever, 2- Leishmaniasis, 3- Lyme disease, 4- Lymphogranuloma ve-nereum (LGV), 5- Nocardiosis, 6- Sarcoidosis, 7- Sporotrichosis, 8- Syphilis, & 9- Toxoplasmosis (Mada *et al,* 2022).

Bartonella henselae must be considered in differential diagnosis of localized lymphadentitis, and the steoarticular pain or limitation with cat-scratch disease in children must be examined for the bone spreading (Donà *et al,* 2018). Radiological differential cat scratch disease diagnosis includes other infections and a range of benign and malignant soft tissue tumors, such as peripheral nerve sheath tumors, synovial sarcoma, leiomyosarcoma, and distant nodal metastasis (Chen *et al,* 2018), as well bone sarcoma due to undefined soft tissue mass without the discernible lymph node structure or bone involvement

(Amerstorfer *et al,* 2021).

Treatment: In general *B. henselae* can cause various human infections, ranges from benign and self-limiting diseases to severe and life-threatening non-treated diseases. Pérez-Martínez *et al.* (2010) in Spain reported that *Bartonella* spp. caused a wide spectrum of emerging and re-emerging infectious diseases, without a universal therapy, and that treatment must be individu-ally chosen. Prutsky *et al.* (2013) in USA concluded that clinical bartonellosis treatment relied mostly on expert opinion and antimicrobial susceptibility data, and that randomized controlled trials are needed to evaluate the different treatment options. Angelakis and Raoult (2014) in France reported that treatment of bartonellosis must be based on its pathogenicity Li *et al.* (2019) in USA reported that among FDA approved drugs, pyrvinium pamoate, daptomycin, methylene blue, clotrimazole, and gentamicin and streptomycin at respective maximum drug concentration in sera (C_{max}) had the capacity to completely eradication of *B. henselae* after 3-day drug exposure in subculture studies. Ma *et al.* (2019) in USA reported that *B. henselae* cause cat scratch disease, endocarditis in humans and animals leads to acute or chronic bacterial persistence. They added that carvacrol and cinnamaldehyde, of oregano and cinnamon bark essential oils, respectively, with the high activity against the stationary phase *B. henselae* such that they were able to eradicate all bacterial cells even at concentration $\leq$ 0.01% (*v/v*). Zheng *et al.* (2020) in China found that antibiotic combinations (azithromycin/cipro-flo xacin, azithromycin/methylene blue, rifampin/ciprofloxacin, rifampin/methylene blue) completely eradicated the *B. henselae* biofilm after 6 days treatment.

In Egypt: Reeves *et al.* (2007) from 14 governorates collected 616 tropical rat mite, *Ornithonyssus bacoti* from *Rattus norvegicus* and *R. rattus* by DNA extracts from mites identified a *Bartonella* spp., *Coxiella burnetii*, and 2 *Rickettsia* spp. by PCR amplification and sequencing in eight pools. Alsarraf *et al.* (2017) in South Sinai assessed *Bartonella* infection in rodents, with prevalence differed between them as 30.6% in 111 *Dipodillus dasyurus*, 10.8% in 65 *Sekeetamys calurus*, 9.6% in 73 *Acomys russatus* and 3.6% in 837 *A. russatus.* Rodents were trapped in 2000, 2004, 2008, & 2012 in four dry montane wadis around Saint Katherine Town's Mountains. The molecular and phylogenetic analyses led to identification of 2 new species: *Candidatus Bartonella* fadhilae and C. *B. sanaae*. The wild rodents and others of Order Rodentia in Egypt and the Eastern Mediterranan Countries were illustratively described (Osborn and Helmy, 1980), with specific key of rodents in Sinai Peninsula (Morsy *et al,* 1988) and Nile Valley (Richard, 2009). Other reservoir hosts as stray dogs and cats were encountered nearly all over Egypt particularly pet ones (Abdel-Moein *et al,* 2017). Dogs serve as reservoir host of extensive array of bacterial, viral and parasites by the feces, urine, saliva (bites or contaminated scratches), and by acting as source of fleas, lice, tick or mites exposure or reservoir for vector borne diseases (Sabry *et al,* 2012). Also, cats are the main reservoir of toxoplasmosis, and zoonotic *B. henselae* or cat scratch disease and other risky diseases (Sabry *et al,* 2013).

As to bartonellosis' vectors, fleas (45 species) ectoparasites on man and animals were reported allover Egypt by many authors (Mikhail *et al,* 2011) and standard keys were given (Hoogstraal, 1956). Lice (human 3 species) apart from non-human ones were reported by many authors on man mainlly child ren (Morsy *et al,* 2001a), causing asthmatic bronchitis (Abou-Gamra *et al,* 1992) as well as on domestic animals (Morsy *et al,* 2001b) and even on bats (Morsy *et al,* 1986). Sandflies up to 9 species of *Phlebotomus* were reported (Saleh *et al,* 2015). Ticks (44) gene ra & species were encountered allover Egypt infesting man, domestic and wild animals as well as birds (Okely *et al,* 2022).

Again, El-Kholy *et al.* (2015) in Cairo University 132 patients were diagnosed as infe-

ctive endocarditis. Eleven patients with blood culture-negative endocarditis BCNE (8.3 %) were PCR diagnosed as zoonotic endocarditis as five brucellosis cases, four bartonellosis cases and two *Coxiella burnetii* cases. Al-Kappany *et al.* (2011) in Cairo reported a high prevalence of *T. gondii*, *Bartonella* spp. and feline immunodeficiency virus in cats. Abdullah *et al.* (2021) in Giza reported a potential novel *Bartonella* sp. from cattle and buffaloes, including a new genotype of *Bo. theileri* from cattle. Sayed *et al.* (2022) in Assiut Governorate molecularly identified *B. henselae* in blood 8% (6/75) of cats. Seroprevalence was higher in females (46.6%) than males (41.7%), higher in cat owners 51.4% (19/37) than with a history of contact 42.9% (27/63), and in the rural areas 79.5% (31/39) than in urban ones 24.6% (15/61).

Some Eastern Mediterranan Countries, in Tunisia Znazen *et al.* (2005) reported that patients' endocarditis *Bartonella* accounted to 9.8%. Zouari *et al.* (2017) reported bartonellosis in dog flea, *Ctenocephalides canis* a zoonotic species. They added that the medical practitioners and farmers must be apprised with the presence of *Bartonella* in fleas and implement preventive measures.

In Algeria, Kernif *et al.* (2010) reported *Bartonella* DNA extracted in blood samples from the domestic dogs. Bitam *et al.* (2012) molecularly reported *B. elizabethae* and *B. clarridgeiae* in fleas collected on seven hedgehogs, *B. tribocorum* and *B. elizabethae* in fleas collected from 26 rats and mice, and *B. rochalimae* detected in fleas collected on *R. norvegicus.* Selmi *et al.* (2021) detected *Anaplasma, Rickettsia,* and *Bartonella* in wild rodents especially in alongside domestic livestock and man.

Chomel *et al.* (2012) in USA reported so many zoonotic *Bartonella* spp. in Iraq imported sick dogs. In Lebanon, Matar *et al.* (1999) by PCR-RFLP-based assay early diagnosed suspected zoonotic *Bartonella* spp. Nba *et al.* (2011) detected *Rickettsia felis* in 17 (16%) and *B. henselae* in three *Ctenocephalides felis* (2.9%).

In Morocoo, Boudebouch*et al.* (2011) detected *B. henselae*, an agent of cat scratch disease; and *Bartonella clarridgeiae*, a cat pathogen and potentially a human pathogen.

In Saudi Arabia, Kleynhans *et al.* (2018) by multiple *Bartonella* lineages incriminated *Gerbillus nanus* is a natural reservoir. Alanazi *et al.* (2020) reported that *B. henselae* and *A. platys* are known zoonotic pathogens; detected by PCR 46/70 dogs (65.7%) from Asir Province were positive for at least one of *Anaplasma* spp., *Babesia* spp., *Bartonella* spp., & *Mycoplasma* spp. But, 17/44 cats (38.6%) tested positive after MT-PCR showed a higher rate of *M. haemofeis*/*M. haemocanis* (13.6%) & *Candidatus Mycoplasma haemominutum* (13.6%), followed by *B. henselae* (9.1%) and *A. platys* (2.3%).

In Palestinian Territories, Nasereddin ***et*** *al.* (2014) reported the DNA sequencing of *B. clarridgeiae* (50%), *B. henselae* (27%), and *B. koehlerae* (3%) in *C. felis*. They clarified the important role of cat and rat fleas as vectors of zoonotic bartonellosis and the potential pathogenic risk to humans and animals.

Conclusion

Bartonella species are fastidious, gram-negative bacteria causing a range of manifestations including cat scratch disease, bacillary angiomatosis and other infections in patients, and culture-negative endocarditis. But, typical *Bartonella* pathogenesis as the known data focused on its infection of the erythrocytes and vascular endothelial cells. Thus, severity and types of infection correlate with the host's immune function.

Documented human bartonellosis are *B. bacilliformis, B. quintana, & B. henselae* associated with well-defined animals' reservo ir and blood sucking vector interact with endothelial cells and can induce angiogenesis.

Bartonella spp are gram-negative, pleomorphic bacteria very poorly stained in tissues using Gram stain but will be black with silver-impregnated stains. Microbes grow slowly up to seven days; regardless the specific methods used before can be detected.

Cats serve are major reservoir for zoonotic

B. henselae, but infrequently display clinical signs of its infection. Man serves as reservoir for *B. quintana* and *B. bacilliformis*, fleas, lice, sandflies, ticks and others play an important role in zoonotic *Bartonella*. Considering zoonosis from pet cats and dogs and wild animals pose human infections, effective vectors control strategies are advocated.

Recommendations

Undoubtedly, bartonellosis a vector borne in human and animals is a re-emerging infectious in Egypt and neighboring countries.

Current epidemiological data and surveillance of bacterial zoonosis in the country are inadequate, a circumstance that obstructs the progress of one health development.

There is a need for cost-effective strategies that will increase the prioritization of vector-borne bacterial zoonosis in health policies and encourage health interventions.

This overview implementations can likely lead to a reduction in local incidence rates of patients with unknown fever.

Authors' declaration: The authors declare that they have neither conflict of interest nor received fund.

References

Abdel-Mein, KA, El-Hariri, MD, Washy, M O, Samir, A, 2017: Occurrence of ampicillin-resistant *Enterococcus faecium* carrying esp gene in pet animals: An upcoming threat for pets lovers. J. Glob. Antimicrob. Resist. 9:115-7.

Abdullah, HHAM, Elbayoumy, MK, Allam, AM, Ashry, HM, Abdel-Shafy, S, 2021: Molecular epidemiology of certain vector-borne bacterial microorganisms in domestic animals & their ectoparasites in Egypt. Trop. Anim. Hlth. Prod Sep 27;53(5):484. doi: 10.1007/s11250-021-02911-z.

Abou-Gamra, EM, El Shayeb, FA, El Banna, M, Farrag, AMK, Morsy, TA, 1992: Possibility of lice allergy among Egyptian patients with asthmatic bronchitis. J. Egypt. Soc. Parasitol. 22, 1:37-50.

Alanazi, AD, Alouffi, AS, Alyousif, MS, Alshahrani, MY, Abdullah, HHAM, *et al,* 2020: Molecular survey of vector-borne pathogens of dogs and cats in two regions of Saudi Arabia. Pathogens 10, 1:25. doi:10.3390.

Al-Kappany, YM, Lappin, MR, Kwok, OC, Abu-Elwafa, SA, Hilali, M, *et al,* 2011: Seroprevalence of *Toxoplasma gondii* and concurrent *Bartonella* spp., feline immunodeficiency virus, feline leukemia virus & *Dirofilaria immitis* infections in Egyptian cats. J. Parasitol. 97, 2:256-8.

Alsarraf, M, Mohallal, EME, Mierzejewska, E J, Borowczyk, JB, Falęciak, R, *et al,* 2017: Description of *Candidatus Bartonella fadhilae* n. sp. and *Candidatus Bartonella sanaae* n. sp. (*Bartonellaceae*) from *Dipodillus dasyurus* and *Sekeetamys calurus* (*Gerbillinae)* from the Sinai Massif (Egypt) Vect. Borne Zoonot. Dis. 17, 7: 483-94.

Amerstorfer, F, Igrec, J, Valentin, T, Leithner, A, Leitner, L, *et al,* 2021: Cat at home? Cat scratch disease, with atypical presentations, and aggressive radiological findings mimicking sarcoma, a potential diagnostic pitfall. Acta Orthop. 92, 6:753-9.

Anderson, B, 2001: The interactions of *Bartonella* with endothelial cells and erythrocytes. Trend. Microbiol. 9, 11:530-2.

Andric, B, Velkovski, A, Jovanovic, M, Markovic, M, Golubovic, M, 2018: Increased risk of *Bartonella* infections in humans. Open J. Clin. Diag. 8:3, September DOI: 10.4236/ojcd. 83004

Angelakis, E, Raoult, D, 2014: Pathogenicity and treatment of *Bartonella* infections. Int. J. Antimicrob. Agents 44, 1:16-25.

Angelakis, E, Diatta, G, Abdissa, A, Trape, J F, Mediannikov, O, *et al,* 2011a: Altitude-dependent presence of *Bartonella quintana* in genotype C head lice from Ethiopia. Emerg. Infect. Dis. 17:2357-9.

Angelakis, E, Rolain, JM, Raoult, D, Brouqui, P, 2011b: *Bartonella quintana* in head louse nits. FEMS Immunol. Med. Microbiol. 62, 2: 244-6.

Arvand, M, Ignatius, R, Regnath, T, *et al,* 2001: *Bartonella henselae*-specific cell-mediated immune responses display a predominantly Th1 phenotype in experimentally infected C57-BL/6 mice. Infect. Immun. 69:6427-32.

Avidor, B, Graidy, M, Efrat, G, *et al,* 2004: *Bartonella koehlerae*, a new cat-associated agent of culture-negative human endocarditis. J. Clin. Microbiol. 42:3462-6.

Bass, JW, Vincent, JM, Person, DA, 1997: Expanding spectrum of bartonella infections. II. Cat scrach disease. Pediatr. Infect. Dis. J. 16:157-63

Birtles RJ, Raoult D, 1996: Comparison of partial citrate synthase gene (gltA) sequences for phylogenetic analysis of *Bartonella* species. Int.

J. Syst. Bacteriol. 46:891-89

Birtles, RJ, Canales, JA, Ventosilla, P, *et al,* 1999: Survey of *Bartonella* species infecting intradomicillary animals in Huayllacallán Valley, Ancash, Peru, a region endemic for human bartonellosis. Am. J. Trop. Med. Hyg. 60:799-804.

Birtles, RJ, Raoult, D, 1996: Comparison of partial citrate synthase gene (gltA) sequences for phylogenetic analysis of *Bartonella* species. Int. J. Syst. Bacteriol. 46:891-6.

Bitam, I, Rolain, JM, Nicolas, V, Tsai, YL, Parola, P, *et al,* 2012: A multi-gene analysis of diversity of *Bartonella* detected in fleas from Algeria. Comp. Immunol. Microbiol. Infect. Dis. 35, 1:71-6.

Boudebouch, N, Sarih, M, Beaucournu, JC, Amarouch, H, Hassar, M, *et al,* 2011: *Bartonella clarridgeiae, B. henselae* and *Rickettsia felis* in fleas from Morocco. Ann. Trop. Med. Parasi ol. 105, 7:493-8

Bonilla, DL, Kabeya, H, Henn, J, *et al,* 2009: *Bartonella quintana* in body lice and head lice from homeless persons, San Francisco, California, USA. Emerg. Infect. Dis. 15:912-6.

Breitschwerdt, EB, 2017: Bartonellosis, one health and all creatures great and small. Vet. Dermatol. 28:96-e21

Breitschwerdt, EB, Hegarty, BC, Hancock, S I, 1998: Sequential evaluation of dogs naturally infected with *Ehrlichia canis, Ehrlichia chaffeensis, Ehrlichia equi, Ehrlichia ewingii,* or *Bartonella vinsonii*. J. Clin. Microbiol. 36:2645-8.

Breitschwerdt, EB, Kordick, DL, 2000: *Bartonella* infection in animals: Carrier-ship, reservoir potential, pathogenicity, and zoonotic potential for human infection. Clin. Microbiol. Rev. 13:428-32.

Brenner, DJ, O'Connor, SP, Winkler, HH, Steigerwalt, AG, 1993: Proposals to unify the genera *Bartonella* and *Rochalimaea*, with descriptions of *Bartonella quintana* comb. nov., *Bartonella vinsonii* comb. nov., *Bartonella henselae* comb. nov., and *Bartonella elizabethae* comb. nov., and to remove the family *Bartonellaceae* from the order Rickettsiales. Int. J. Syst. Bacteriol. 43:777-81.

Brouqui, P, Raoult, D, 1996: Bartonella quintana invades and multiplies within endothelial cells in vitro and in vivo and forms intracellular blebs. Res. Microbiol. 147:719-24.

Buffet, JP, Kosoy, M, Vayssier-Taussat, M, 2013: Natural history of *Bartonella*-infecting rodents in light of new knowledge on genomics, diversity and evolution. Fut. Microbiol. 8:1117-28.

Capo, C, Amirayan-Chevillard, N, Brouqui, P, *et al,* 2003: *Bartonella quintana* bacteremia and ov-erproduction of interleukin-10: Model of bacterial persistence in homeless people. J. Infect. Dis. 187: 837-42.

CDC, 2022: *Bartonella* infection. Home *Bartonella* CDC https://www.cdc.gov › *bartonella*

Chaloner, GL, Harrison, T, Birtles, RJ, 2013: *Bartonella* species as a cause of infective endocarpditis in the UK. Epidemiol. Infect. 141, 4: 841-6.

Chang, CC, Chomel, BB, Kasten, RW, *et al,* 2002: Molecular epidemiology of *Bartonella henselae* infection in human immunodeficiency virus-infected patients and their cat contacts, using pulsed-field gel electrophoresis and genotyping. J. Infect. Dis. 186:1733-7.

Chen, Y, Fu, Y-B, Xu, X-F, Pan, Y, Lu, C-Y, *et al,* 2018: Lymphadenitis associated with cat-scratch disease simulating a neoplasm: Imaging findings with histopathological associations. Oncol. Lett. 15, 1:195-204.

Chomel, BB, Abbott, RC, Kasten, RW, *et al,* 1995: *Bartonella henselae* prevalence in domestic cats in California: Risk factors and association between bacteremia and antibody titers. J. Clin. Microbiol. 33:2445-50.

Chomel, BB, Kasten, RW, 2010: Bartonellosis, an increasingly recognized zoonosis. J. Appl. Microbiol. 109:743-50.

Chomel, BB, McMillan, AC, Kasten, RW, Stuckey, MJ, Sato, S, *et al,* 2012: *Candidatus Bartonella merieuxii*, a potential new zoonotic Bartonella species in canids from Iraq. PLoS Negl. Trop. Dis. 6, 9:e1843. doi: 10.1371/

Colson, P, Lebrun, L, Drancourt, M, Boue, F, Raoult, D, *et al,* 1996: Multiple recurrent bacillary angiomatosis due to *Bartonella quintana* in an HIV-infected patient. Eur. J. Clin. Microbiol. Infect. Dis. 15:178-80.

Comer, JA, Diaz, T, Vlahov, D, *et al,* 2001: Evidence of rodent-associated *Bartonella* and *Rickettsia* infections among intravenous drug users from Central and East Harlem, New York City. Am. J. Trop. Med. Hyg. 65:855-9.

Corduneanu, A, **Sándor, AD, Ionică, M, Hornok, S, Leitner, N, *et al,* 2018:** *Bartonella* DNA in heart tissues of bats in central and eastern Europe and a review of phylogenetic relations of bat-associated bartonellae. Parasit Vectors Aug 29;11(1):489. doi: 10.1186/s13071-018-3070-7**.**

Cunningham, ET, Koehler, JE, 2000: Ocular bartonellosis. Am. J. Ophthalmol. 130, 3:340-9.
Daly, JS, Worthington, MG, Brenner, DJ, *et al,* 1993: *Rochalimaea elizabethae* sp. nov. isolated from a patient with endocarditis. J. Clin. Microbiol. 31:872-6.
Dehio, C, 2003: Recent progress in understanding *Bartonella*-induced vascular proliferation. Curr. Opin. Microbiol. 6:61-6.
Dehio, C, 2008: Infection-associated type IV secretion systems of *Bartonella* and their diverse roles in host cell interaction. Cell Microbiol. 10: 1591-6.
Dehio, C, Meyer, M, Berger, J, *et al,* 1997: Interaction of *Bartonella henselae* with endothelial cells results in bacterial aggregation on the cell surface and the subsequent engulfment and internalisation of the bacterial aggregate by a unique structure, the invasome. J. Cell Sci.110 (Pt 18): 2141-8.
Diatta, G, Mediannikov, O, Sokhna, C, Bassene, H, Socolovschi, C, *et al,* 2014: Short Report: Prevalence of *Bartonella quintana* in patients with fever and head lice from rural areas of Sine-Saloum, Senegal. Am. J. Trop. Med. Hyg. 91, 2:291-3.
Diaz, MH, Baty, Y, Malania, L, Winchell, JM, Kosay, MY, 2012: Development of a novel genus species and genotypes. J. Clin. Microbiol. 50: 1186-90.
Donà, D, Fovino, NL, Mozzo, E, Cabrelle, G, Bordin, G, *et al,* 2018: Osteomyelitis in cat-scratch disease: A never-ending dilemma; a case report and literature review. Case Rep. Pediatr. 2018:1679306
Drancourt, M, Birtles, R, Chaumentin, G, *et al,* 1996: New serotype of *Bartonella henselae* in endocarditis and cat-scratch disease. Lancet 347: 441-5.
Droz, S, Chi, B, Horn, E, *et al,* 1999: *Bartonella koehlerae* sp. nov., isolated from cats. J. Clin. Microbiol. 37:1117-20.
Duncan, A, 2007: A combined approach for the enhanced detection and isolation of *Bartonella* species in dog blood samples: Pre-enrichment liquid culture followed by PCR a& subculture onto agar plates. J. Microbiol. Meth. 69, 2:273-81.
Edouard, S, Nabet, C, Lepidi, H, Fournier, P E, Raoult, D, 2015: *Bartonella*, a common cause of endocarditis: A report on 106 cases and review. J. Clin. Microbiol. 53, 3:824-9
Eicher, SC, Dehio, C, 2012: *Bartonella* entry mechanisms into mammalian host cells. Cell Microbiol. 14:1166-70.
Eiger-Moscovich, M, Amer, R, Oray, M, Tabbara, KF, Tugal-Tutkun, I, *et al,* 2016: Retinal artery occlusion due to *Bartonella henselae* infection: A case series. Acta Ophthalmol. 94, 5: e367-70.
El Hamzaoui, B, Laroche, M, Bechah, Y, Bérenger, JM, Parola, P, 2019: Testing the competence of *Cimex lectularius* bed bugs for the transmission of *Borrelia recurrentis*, the agent of relapsing fever. Am. J. Trop. Med. Hyg. 100, 6: 1407-12.
El-Kholy, AA, El-Rachidi, NG, El-Enany, M G, AbdulRahman, EM, Mohamed, RM, *et al,* 2015: Impact of serology and molecular methods on improving the microbiologic diagnosis of infective endocarditis in Egypt. Infection 43, 5: 523-9.
Ellis, BA, Regnery, RL, Beati, L, *et al,* 1999: Rats of the genus *Rattus* are reservoir hosts for pathogenic *Bartonella* species: An Old World origin for a New World disease? J. Infect. Dis. 180:220-4.
Eremeeva, ME, Gerns, HL, Lydy, SL, *et al,* 2007: Bacteremia, fever, and splenomegaly caused by a newly recognized bartonella species. N. Engl. J. Med. 356:2381-6.
Foucault, C, Barrau, K, Brouqui, P, Raoult, D, 2002: *Bartonella quintana* bacteremia among homeless people. Clin. Infect. Dis. 35:684-8.
Foucault, C, Brouqui, P, Raoult, D, 2006: *Bartonella quintana* characteristics and clinical management. Emerg. Infect. Dis. 12:217-20.
Greub, G, Raoult, D, 2002: *Bartonella*: New explanations for old diseases. J. Med. Microbiol. 51:915-9.
Heller, R, Artois, M, Xemar, V, *et al,* 1997: Prevalence of *Bartonella henselae* and *Bartonella clarridgeiae* in stray cats. J. Clin. Microbiol. 35:1327-30.
Heller, R, Riegel, P, Hansmann, Y, Delacour, G, *et al,* 1998: *Bartonella tribocorum* sp. nov., a new *Bartonella* species isolated from the blood of wild rats. Int. J. Syst. Bacteriol. 48 Pt 4:1333-9.
Hoogstraal, H, 1956: The flea (Siphonaptera) of Egypt: Host-parasite relationship of rodents of the families Spalacidae, Muridae, Gliridae, Dipodidae & Hystricidae. J. Egypt. Pub. Hlth. Assoc. 39:1-35.
Iannino, F, Salucci, S, Di Provvido, A, Paolini, A, Ruggieri, E, 2018: *Bartonella* infections in humans dogs and cats. Vet. Ital. 54:63-72.

Johnson, G, Nelson, S, Petric, M, Tellier, R, 2000: Comprehensive PCR-based assay for detection and species identification of human herpesviruses. J. Clin. Microbiol. 38**:**3274-9

Judson, SD, Frank, HK, Hadly, E, 2015: Bartonellae are prevalent and diverse in Costa Rican Bats and bat Flies. Zoonoses Publ. Hlth. 62, 8: 609-17

Jurja, S, Stroe, AZ, Pundiche, MB, Docu Axelerad, S, Mateescu, G, *et al,* 2022: The clinical profile of cat-scratch disease's neuro-ophthalmological effects. Brain Sci. Feb 4;12 (2):217. Doi: 10.3390/ brainsci12020217.

Kamani, J, Morick, D, Mumcuoglu, KY, Harrus, S, 2013: Prevalence and diversity of *Bartonella* species in commensal rodents and ectoparasites from Nigeria, West Africa. PLoS Negl. Trop. Dis. 7, 5:e2246 Published online May 30.

Kempf, VA, Lebiedziejewski, M, Alitalo, K, *et al,* 2005: Activation of hypoxia-inducible factor-1 in bacillary angiomatosis: Evidence for a role of hypoxia-inducible factor-1 in bacterial infections. Circulation 111:1054-8.

Kempf, VA, Volkmann, B, Schaller, M, *et al,* 2001: Evidence of a leading role for VEGF in *Bartonella henselae*-induced endothelial cell proliferations. Cell Microbiol. 3:623-8.

Kernif, T, Asisi, M, Doumandji, SE, Chomel, BB, Raoult, D, *et al,* 2010: Molecular evidence of *Bartonella* infection in domestic dogs from Algeria, North Africa, by PCR. Am. J. Trop. Med. Hyg. 83, 2:298-300.

Kim, CM, **Kim, JY**, **Yi, YH, Lee, MJ, Cho, M R, *et al,* 2005:** Detection of *Bartonella* species from ticks, mites and small mammals in Korea. J. Vet. Sci. 6, 4:327-34.

Kirby, JE, 2004: In vitro model of *Bartonella henselae*-induced angiogenesis. Infect. Immun. 72:7315-8.

Koehler, JE, Glaser, CA, Tappero, JW, 1994: *Rochalimaea henselae* infection: A new zoonosis with the domestic cat as reservoir. JAMA 271: 531-6.

Koehler, JE, Quinn, FD, Berger, TG, *et al,* 1992: Isolation of *Rochalimaea* species from cutaneous and osseous lesions of bacillary angiomatosis. N. Engl. J. Med. 327:1625-9.

Kordick, DL, Brown, TT, Shin, K, Breitschwerdt, EB, 1999: Clinical and pathologic evaluation of chronic *Bartonella henselae* or *Bartonella clarridgeiae* infection in cats. J. Clin Microbiol. 37:1536-40.

Kordick, DL, Wilson, KH, Sexton, DJ, *et al,* 1995: Prolonged *Bartonella* bacteremia in cats associated with cat-scratch disease patients. J. Clin. Microbiol. 33:3245-9.

Kosoy, M, Morway, C, Sheff, KW, Bai, Y, *et al,* 2008: *Bartonella tamiae* sp. nov., a newly recognized pathogen isolated from three human patients from Thailand. J. Clin. Microbiol. 46: 772-5.

Kosoy, M, Murray, M, Gilmore, RD, Jr, Bai, Y, *et al,* 2003: *Bartonella* strains from ground squirrels are identical to *Bartonella* washoensis isolated from a human patient. J. Clin. Microbi ol. 41:645-50.

Lai, O, Ho, D, Glick, S, Jagdeo, J, 2016: Bed bugs and possible transmission of human pathogens: A systematic review. Arch. Dermatol. Res. 308, 8:531-8.

Larson, AM, Dougherty, MJ, Nowowiejski, DJ, *et al,* 1994: Detection of *Bartonella* (*Rochalimaea*) *quintana* by routine acridine orange staining of broth blood cultures. J. Clin. Microbiol. 32:1492-6.

Leulmi, H, Bitam, I, Berenger, JM, Lepidi, H, Rolain, JM, *et al,* 2015: Competence of *Cimex lectularius* bed bugs for the transmission of *Bartonella quintana*, the agent of trench fever. PLoS Negl. Trop. Dis. May; 9(5): e0003789. Published online May 22.

Leulmi, H, Bitam, I, Berenger, JM, Lepidi, H, Rolain, JM, *et al,* 2015: *Competence of Cimex lectularius* bed bugs for the transmission of *Bartonella quintana*, the Agent of Trench Fever. PLoS Negl. Trop. Dis. 9, 5:e0003789.

Li, T, **Feng, J, Xiao, S, Shi, W, Sullivan, D, *et al,* 2019:** Identification of FDA-approved drugs with activity against stationary phase *Bartonella henselae*. Antibiotics (Basel). Apr 29;8(2):50. doi:10.3390 /antibiotics8020050.

Lin, EY, Tsigrelis, C, Baddour, LM, Lepidi, H, Rolain, JM, *et al,* 2010: *Candidatus Bartonella mayotimonensis* and endocarditis. Emerg. Infect. Dis. 16:500-3

Lin, JW, Chen, CY, Chen, WC, Chomel, BB, *et al,* 2008: Isolation of *Bartonella* species from rodents in Taiwan including a strain closely related to *Bartonella rochalimae* from *Rattus norvegicus*. J. Med. Microbiol. 57:1496-501.

Lins, KA, Drummond, MR, Velho, PN, 2019: Cutaneous manifestations of bartonellosis. An. Bras. Dermatol. 94, 5:594-602.

Lozano-Sardaneta, YN, Colunga-Salas, P, Sánchez, S, Cáceres, AG, Becker, I, 2019: First report of *Bartonella* sp. in sand flies (Diptera: Psy-

chodidae: Phlebotominae) from Southern Mexico. J. Am. Mosq. Cont. Assoc. 35, 3:224-7.
Lynch, T, Iverson, J, Kosoy, M, 2011: Combining culture techniques for *Bartonella*: The best of both worlds. J. Clin. Microbiol. 49:1363-8.
Ma, X, Shi, W, Zhang, Y, 2019: Essential oils with high activity against stationary phase *Bartonella henselae*. Antibiotics (Basel). Nov 30; 8 (4):246. doi: 10.3390/antibiotics8040246
Mada, PK, Zulfiqar, H, Chandranesan, AS, 2022: Bartonellosis. StatPearls [Internet].
Maggi, RG, Duncan, AW, Breitschwerdt, EB, 2005: Novel chemically modified liquid medium that will support the growth of seven bartonella species. J. Clin. Microbiol. 43:2651-4.
Maggi, RG, Duncan, AW, Breitschwerdt, EB, 2005: Novel chemically modified liquid medium that will support the growth of seven *Bartonella* species. J. Clin. Microbiol. 43:2651-5
Maggi, RG, Kosoy, M, Mintzer, M, Breischwerdt, EB, 2009: Isolation of *Candidatus Bartonella melophagi* from Human Blood. Emerg. Infect.Dis. 15:66-8.
Maguiña, C, Garcia, P, Gotuzo, E, *et al,* 2001: Bartonellosis (Carrion's Disease) in the modern era. CID 33:772-9.
Margileth, AM, 2000: Recent advances in diagnosis and treatment of cat scratch disease. Curr. Infect. Dis. Rep. 2:141-4.
Margileth, AM, Baehren, DF, 1998: Chest-wall abscess due to cat-scratch disease (CSD) in an adult with antibodies to *Bartonella clarridgeiae*: Case report and review of the thoracopulmonary manifesta-tions of CSD. Clin. Infect. Dis. 27: 353-6.
Matar, GM, Koehler, JE, Malcolm, G, Lambert-Fair, MA, Tappero, J, *et al,* 1999: Identification of *Bartonella* species directly in clinical specimens by PCR-restriction fragment length polymorphism analysis of a 16S rRNA gene fragment. J. Clin. Microbiol. 37, 12:4045-7.
Mba, PA, Marié, JL, Rolain, JM, Davoust, B, Beaucournu, JC, *et al,* 2011: *Rickettsia felis* and *Bartonella henselae* in fleas from Lebanon. Vector Borne Zoonotic Dis. 11, 7:991-2.
Mernaugh, G, Ihler, GM, 1992: Deformation factor: An extracellular protein synthesized by *Bartonella bacilliformis* that deforms erythrocyte membranes. Infect. Immun. 60:937-9.
Mikhail MW, Soliman, MI, Morsy, TA, 2011: The current status of fleas according to environmental changes in some governorates in Egypt. J. Egypt. Soc. Parasitol. 41, 1:199-213.
Minnick, MF, Mitchell, SJ, McAllister, SJ, 1996: Cell entry and the pathogenesis of *Bartonella* infections. Trends Microbiol. 4:343-6.
Morse, SF, Olival, KJ, Kosoy, M, Billeter, S, Patterson, B, *et al,* 2012: Global distribution & genetic diversity of *Bartonella* in bat flies (Hippoboscoidea, Streblidae, Nycteribiidae). Infect. Genet. Evol. 12, 8:1717-23.
Morsy, TA, Abou El-Ela, RGh, Abdelmawla, MYM, Khalaf, SAA, 2001a: The prevalence of lice infesting students of primary, preparatory and secondary schools in Cairo, Egypt. J. Egypt. Soc. Egypt. 31, 1:43-50.
Morsy, TA, Habib, KhSM, Haridy, FM, 2001 b: Ivermectin and clorsulon (ivomec super) in treatment of goats naturally infested with scab mites and biting lice. J. Egypt. Soc. Parasitol. 31, 2:373-9.
Morsy, TA, Khalid, MLM, Bebars, MA, Abdel Hamid, MY, 1986: Arthropod ectoparasites on some Egyptian bats. J. Egypt. Soc. Parasitol. 16, 2:525-30.
Morsy, TA, Shoukry, A, El Kady, GA, 1988: A review and distribution map of rodents in Sinai, Egypt. J. Egypt. Soc. Parasitol. 18, 2:683-92.
Mulinsk, KE, Hang, J, Jiang, J, *et al,* 2013: Molecular typing of *Candidates bartonella ancashi*, a new human pathogen causing *Verruga peruana*. J. Clin. Microbiol. 51:3865-81.
Müller, A, Reiter, M, Schötta, AM, Stockinger, H, Stanek, G, 2016: Detection of *Bartonella* spp. in *Ixodes ricinus* ticks and *Bartonella* seroprevalence in human populations. Ticks Tick Borne Dis. 7, 5: 763-7.
Musso, T, Badolato, R, Ravarino, D, *et al,* 2001: Interaction of *Bartonella henselae* with the murine macrophage cell line J774: Infection and proinflammatory response. Infect. Immun. 69:5974-6.
Nasereddin, A, **Risheq, A, Harrus, S, Azmi, K, Ereqat, S, *et al,* 2014**: Bartonella species in fleas from Palestinian territories: Prevalence and genetic diversity. J. Vector Ecol. 39, 2:261-70
Nawrocki, CC, Max, RJ, Marzec, NS, Nelson, CA, 2020: Atypical manifestations of cat-scratch disease, United States, 2005-2014 Emerg. Infect. Dis. 26, 7:1438-46.
Neves, P, Cintra, ML, Uthida-Tanaka, AM, *et al,* 2003: What do we (not) know about the human bartonelloses?. Braz. J. Inf. Dis. 7, 1:1-6.
Okaro, U, Addisu, A, Casanas, B, Anderson, B, 2017: *Bartonella* species, an emerging cause

of blood-culture-negative endocarditis. Clin. Microbiol. Rev. 30, 3:709-46.

Okely, M, Chen, Z, Rabia Anan, R, Gad-Allah, S, 2022: Updated checklist of the hard ticks (Acari: Ixodidae) of Egypt, with notes of livestock host and tick-borne pathogens: Systemic and Applied Acarology ISSN 1362-1971 (Print); ISSN 2056-6069 (Online)

O'Reilly, KL, Bauer, RW, Freeland, RL, *et al,* 1999: Acute clinical disease in cats following infection with a pathogenic strain of *Bartonella henselae* (LSU16). Infect. Immun. 67:3066-9.

Osborn, DJ, Helmy, I, 1980: The Contemporary Land Mammals of Egypt (Including Sinai). Fieldiana Zoology: Published by Field Museum of Natural History.

Pape, M, Kollaras, P, Mandraveli, K, *et al,* 2005: Occurrence of *Bartonella henselae* and *Bartonella quintana* among human immunodeficiency virus-infected patients. Ann. N Y Acad. Sci.1063:299-302.

Perez, JE, Ogusuko, E, 1995: Historical aspects of the vectors of bartonellosis and leishmaniasis in Peru. Bol. Dir. Malariol. Y. San Amb. 35:277-94.

Pérez-Martínez, L, Blanco, J, Oteo, JA, 2010: Treatment of human infections caused by *Bartonella* spp. Rev. Esp. Quimioter. 23, 3:109-14.

Podsiadly, E, Chmielewski, T, Tylewska-Weirzbanowska, S, 2003: *Bartonella hensellae* and *Borrelia burgdorferi* infections of the central nervous system. Ann. New York Acad. Sci. 990: 404-6.

Popa, C, Abdollahi-Roodsaz, S, Joosten, LA, *et al,* 2007: *Bartonella quintana* lipopolysaccharide is a natural antagonist of Toll-like receptor 4. Infect. Immun. 75:4831-5.

Portillo, A, Maggi, R, Oteo JA, Bradley, J, García, L, *et al,* 2020: *Bartonella* spp. prevalence (serology, culture, & PCR) in sanitary workers in La Rioja Spain. Pathogens Mar; 9(3): 189. Online Mar 4. Doi: 10.3390/pathogens9030189

Prutsky, G, Domecq, JP, Mori, L, Bebko, S, Matzumura, M, *et al,* 2013: Treatment outcomes of human bartonellosis: A systematic review & metaanalysis. Int. J. Infect. Dis. 17, 10:e81-9.

Randell, MG, Balakrishnan, N, Christie, GR, Mackin, A, Breitschwerdt, EB, 2018: *Bartonella henselae* infection in a dog with recalcitrant ineffective erythropoiesis. Vet. Clin. Pathol. 47: 45-50.

Raoult, D, **Roux, V, 1999:** Body louse as a vector of reemerging human diseases. Clin. Infect. Dis. 29, 4:888-911.

Raoult, D, Fournier, PE, Drancourt, M, *et al,* 1996: Diagnosis of 22 new cases of *Bartonella* endocarditis. Ann. Intern. Med. 125:646-9.

Raoult, D, Roblot, F, Rolain, JM, *et al,* 2006: First isolation of *Bartonella alsatica* from a valve of a patient with endocarditis. J. Clin. Microbiol. 44:278-82.

Reeves, WK, **Loftis, AD, Szumlas, DE, Abbassy, MM, Helmy, IM, *et al,* 2007:** Rickettsial pathogens in the tropical rat mite *Ornithonyssus bacoti* (Acari: Macronyssidae) from Egyptian rats (*Rattus* spp.). Exp. Appl. Acarol. 41, 1/2: 101-7.

Regnery, RL, Childs, JE, Koehler, J, 1995: Infections associated with *Bartonella* species in persons infected with human immunodeficiency virus. Clin. Infect. Dis. 21, 1:S94-8

Resto-Ruiz, S, Burgess, A, Anderson, BE, 2003: The role of the host immune response in pathogenesis of *Bartonella henselae*. DNA Cell Biol. 22:431-6.

Richard, H, 2009: A Field Guide to the Mammals of Egypt: American University in Cairo Press.

Riess, T, Andersson, S, Lupas, A, *et al,* 2004: *Bartonella* adhesin a mediates a proangiogenic host cell response. J. Exp. Med. 200:1267-70.

Rolain, JM, Arnoux, D, Parzy, D, *et al,* 2003: Experimental infection of human erythrocytes from alcoholic patients with *Bartonella quintana* Ann. N Y Acad. Sci. 990:605-8.

Rolain, JM, Brouqui, P, Koehler, JE, *et al,* 2004: Recommendations for treatment of human infections caused by *Bartonella* species. Antimicrob. Agents Chemother. 48:1921-5.

Rossi, MA, Balakrishnan, N, Linder, KE, Messa, JB, Breitschwerdt, EB, 2015: Concurrent *Bartonella henselae* infection in a dog with panniculitis and owner with ulcerated nodular skin lesions. Vet. Dermatol. 26:60-3.

Roux, V, **Raoult, D, 1995:** Inter- and intraspecies identification of *Bartonella* (*Rochalimaea*) species. J. Clin. Microbiol. 33, 6:1573-9.

Roux, V, Eykyn, S, Wyllie, S, Raoult, D, 2000: *Bartonella vinsonii* subsp. *berkhoffii* as an agent of afebrile blood culture-negative endocarditis in a human. J. Clin. Microbiol. 38:1698-702.

Sabry, AA, Fouad, MAH, Morsy, ATA, 2013: Zoonoses from cats: With special reference to Egypt. J. Egypt. Soc. Parasitol. 43, 1:429-46.

Sabry, AA, Morsy, ATA, Morsy, TA, 2012: Zoonoses from dogs with special reference to

Egypt. J. Egypt. Soc. Parasitol. 42, 3:583-604.
Saenz, HL, Engel, P, Stoeckli, MC, *et al,* 2007: Genomic analysis of *Bartonella* identifies type IV secretion systems as host adaptability factors. Nat. Genet. 39:1469-75.
Saleh, AMA, Labib, NA, Abdel-Fattah, MS, Al-Attar, MB, Morsy, TA, 2015: Sandfly *Phlebotomus papatasi* (Phlebotominae): A general review with special reference to zoonotic cutaneous leishmaniasis in Egypt. JESP 45, 3:525-44.
Sayed, ASM, Alsaadawy, RM, Ali, MM, Abd El-Hamid, RF, Baty, RS, 2022: Serological and mol-ecular detection of *Bartonella henselae* in cats and humans from Egypt: Current status and zoonotic implications. Front. Vet. Sci. Apr 14; 9: 859104. doi: 10.3389/fvets.2022.859104
Selmi, R, Belkahia, H, Dhibi, M, Abdelaali, H, Lahmar, S, *et al,* 2021: Zoonotic vector-borne bacteria in wild rodents and associated ectoparasites from Tunisia. Infect. Genet. Evol. Nov; 95:105039. doi: 10.1016/
Spach, DH, Kanter, AS, Daniels, NA, *et al,* 1995: *Bartonella* (*Rochalimaea*) species as a cause of apparent "culture-negative" endocarditis. Clin. Infect. Dis. 20:1044-7.
Spach, DH, Koehler, JE, 1998: *Bartonella*-associated infections. Infect. Dis. Clin. North Am. 12:137-42.
Sytykiewicz, H, Karbowiak, G, Werszko, J, Czerniewicz, P, Sprawka, I, Mitrus, J, 2012: Molecular screening for *Bartonella henselae* and *Borrelia burgdorferi* sensu lato co-existence wi-in *Ixodes ricinus* populations in central and eastern parts of Poland. Ann. Agric. Environ. Med. 19, 3:451-6.
Szewczyk, T, Werszko, J, Slivinska, K, Laskowski, Z, Karbowiak, G, 2021: Molecular detection of *Bartonella* spp. in rodents in chernobyl exclusion zone, Ukraine. Acta Parasitol. 66, 1: 222-7.
Telford, SR 3rd, Wormser, GP, 2010: *Bartonella* spp. transmission by ticks not established. Emerg. Infect. Dis. 16:379-82.
Trape, JF, Raoult, D, 2012: *Bartonella quintana* in head lice from Senegal. Vector Bor. Zoon. Dis. 12:1-4.
Vayssier-Taussat, M, Moutailler, S, Femenia, F, Raymond, P, *et al,* 2016: Identification of n novel zoonotic activity of *Bartonella* spp., France. Emerg. Infect. Dis. 22:457-62.
Vermeulen, MJ, Herremans, M, Verbakel, H, Bergmans, AM, Roord, JJ, *et al,* 2007: Serological testing for *Bartonella henselae* infections in The Netherlands: Clinical evaluation of immunofluorescence assay and ELISA. Clin. Microbiol. Infect. 13:627-34.
Versalovic, J, Carroll, KC, Funke, G, Jorgensen, JH, Landry, ML, *et al,* 2011: Manual of Clinical Microbiology, 10th Edition, ASM Press.
Vesty, A, Henderson, G, Blakiston, M, Chhibber, AV, Fox-Lewis, A, *et al,* 2022: Evaluation of ssrA-targeted real time PCR for the detection of *Bartonella* species in human clinical samples and reflex sequencing for species-level identification. Pathology 54, 4:449-52
Welch, DF, Hensel, DM, Pickett, DA, *et al,* 1993: Bacteremia due to *Rochalimaea henselae* in a child: Practical identification of isolates in the clinical laboratory. J. Clin. Microbiol. 31: 2381-4.
WHO, 2018: Vector-Borne Diseases. Available online at: http://www.who.int/en/news-room/fact-sheets/detail/vector-borne-diseases.
Wong, MT, Thornton, DC, Kennedy, RC, Dolan, MJ, 1995: A chemically defined liquid medium that supports primary isolation of *Rochalimaea* (*Bartonella*) ***henselae*** from blood and tissue specime- ns. J. Clin. Microbiol. 33:742-6.
Zheng, X, Ma, X, Li, T, Shi, W, Zhang, Y, 2020: Effect of different drugs and drug combinations on killing stationary phase and biofilms recovered cells of *Bartonella henselae* in vitro. BMC Microbiol. Apr 10;20(1):87.doi: 10.1186/s12866-020-01777-9.
Znazen, A, Rolain, JM, Hammami, N, *et al,* 2005: High prevalence of *Bartonella quintana* endocarditis in Sfax Tunisia. Am. J. Trop. Med. Hyg. 72:503-7.
Zouari, S, Khrouf, F, M'ghirbi, Y, Bouattour, A, 2017: First molecular detection and characterization of zoonotic *Bartonella* species in fleas infesting domestic animals in Tunisia. Parasit. Vectors 10: 436.doi: 10.1186/s13071-017-2372-5.
Kleynhans, DJ, Sarli, J, Hatyoka, LM, Alagaili, AN, Bennett, NC, *et al,* 2018: Molecular assessment of *Bartonella* in *Gerbillus nanus* from Saudi Arabia reveals high levels of prevalence, diversity and co-infection. Infect Genet. Evol. 65:244-50.