Review Article

Query Fever: An Intracellular Pathogenic Bacterial Disease

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Abstract

Coxiella burnetii harmful pathogenic gram - negative coccobacilli, they are exacting intracellular parasites of creature and may likewise contaminate human. Query fever is a pathogenic zoonotic disease or illness, principally influencing goats, sheep, cows and different creatures and communicated to people by utilize tainted creatures meat or through ingestion of their products. Query fever previously depicted by Derrick in 1937 in Australia (Queensland). A particular intracellular bacterium of guinea pigs was disconnected and was attacked and blood collected from Derrick's patients, which was named as Rickettsia *burnetii* by Macfarlane Burnet and Mavis Freeman. Now-a-days it excess of 1000000 new instances of a Query fever happen every year all around the globe. Backslide of the ailment is one of the most significant difficulties. The most significant explanation behind the backslide of Query fever is the endurance of the microscopic organisms inside the macrophages, which makes them safe from the invulnerable framework and upsets the medication conveyance component.

Keywords: Query fever, zoonotic disease, *Coxiella burnetii*, intracellular parasites.

Introduction

Q fever, also known as query fever, is mainly a bacterial infection which principally influences sheep, goats, cows, dog, birds, rodents, cat, and ticks [1]. Causative organism of this disease or illness is *Coxiella burnetii* a Gram - negative coccobacilli. Milk, birth products, faces and urine of infected animals carries these bacteria. Liver, lung and heart are the primary organs usually affected by Q fever. Although a very few organisms of *C. burnetii are* able to cause disease, they are strongly infectious in nature.

C. burnetii can retain its viability and virulence for a longer period of time due to its spore like life cycle. By exposing to the contaminated droplets and raw milk of infected animal, human get infected by Q fever. Spreading of this disease form one human to another is rare which involves exposure to infected women placenta and transfusions of blood from contaminated person to healthy person [2].

In humans, identification of acute *C. burnetii* infection is very difficult because in most of the cases it's remains asymptomatic or shows symptoms which are similar with an atypical pneumonia or influenza-like illness. In case of patients having pre-existing cardiac disease, *C. burnetii* shows devastating effect. Due to presence of its potential infectious nature and having an inhalational route of transmission, *C. burnetii* is considered as a potential agent of bioterrorism. Q fever is categorized as B agent by the Centers for Disease Control and Prevention (CDC).

According to some studies women are less affected than men [2, 3]. *C. burnetii* infection is more found in men than women which might be credited to various employment rates in some particular professions. "In danger" occupations incorporate, however are not restricted to: animal transporters, stockyard workers, veterinary personnel, shearers, farmers, laboratory workers, process kangaroos and people who cull.

Bacteriology

C. burnetii is a tiny gram-negative coccobacillus having 0.2 to 0.4 µm wide and 0.4 to 1 µm length. Although have a gram-negative bacterium like membrane, it is commonly not stainable by the Gram technique. Usually for staining *C. burnetii* the Gimenez method is used in laboratory cultures or clinical specimens (Figure 1). Since *C. burnetii* growth is not

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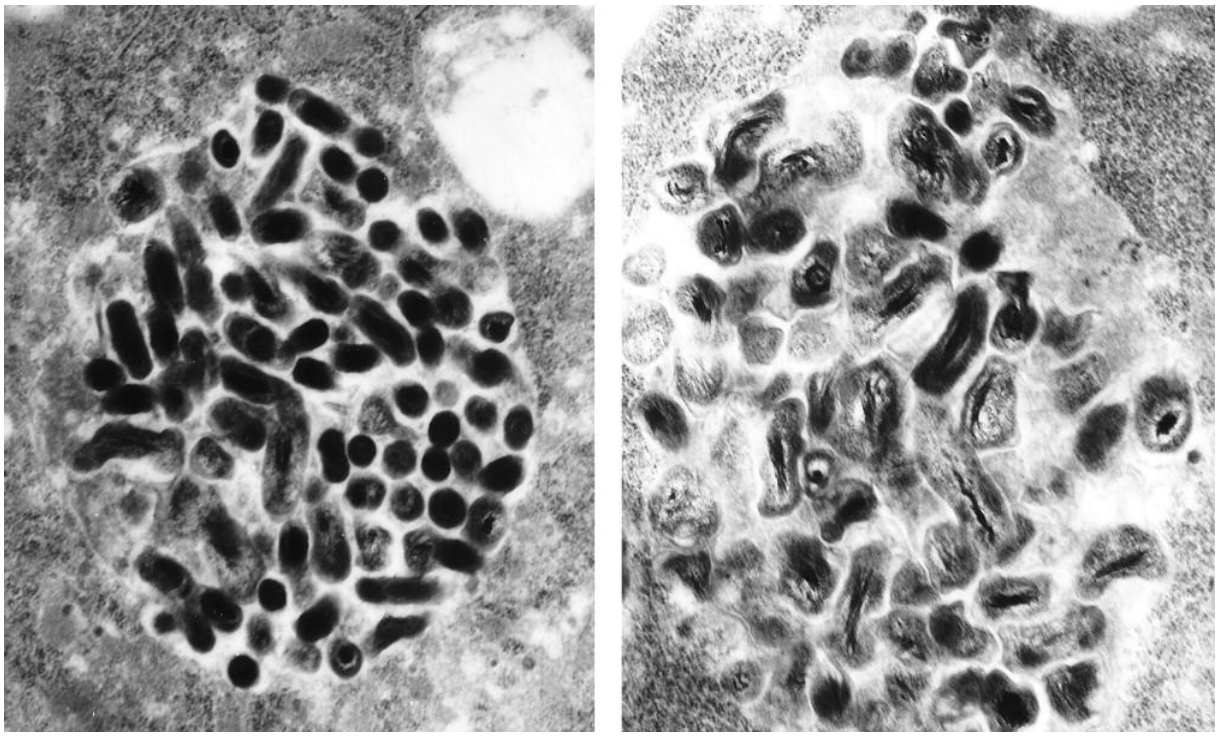

Figure 1: A representative image of the organism *C. burnetii* [6]

occur in axenic medium and has long been recovered from ticks, it has been classified in the Rickettsiales order, the Rickettsiaceae family, and the Rickettsiae tribe together with the genera Rochalimaea and Rickettsia [4]. However, phylogenetic investigations, based mainly on 16S rRNA sequence analysis, have shown that the Coxiella genus belongs to the gamma subdivision of Proteobacteria [5], with the genera Francisella, Legionella, and Rickettsiella as its nearest relatives.

A low degree of genetic heterogeneity is expressed by *C. burnetii* with DNA-DNA hybridized strains. Nonetheless, when DNA from 38 *C. burnetii* disengages was analyzed by restriction fragment length polymorphism (RFLP) examination, six genomic groups (I to VI) were depicted [7]. Afterward, investigation of NotI and SfiI *C. burnetii* DNA restriction fragments by pulsed-field gel electrophoresis (PFGE) brought about the portrayal of four diverse DNA fragment patterns speaking to segregates from genomic groups I, IV, V, and VI [8]. The genome size is profoundly variable among various *C. burnetii* strains, going from 1.5 to 2.4 Mb [9]. The failure to restrict origin function by standard techniques could well be identified with the way that *C. burnetii* most likely has a linear rather than a circular chromosome and in this manner might not have regular bidirectional replication [9]. *C. burnetii* quality arrangements partially or totally accessible in the GenBank or EMBL databases incorporate 23 chromosomal sequences and 17 plasmid sequences. The *C. burnetii* genome involves facultatively a 36-to 42-kb plasmid, whose capacity stays dubious. *C. burnetii* shows antigenic varieties like the smooth-unpleasant variation in the family Enterobacteriaceae. Stage variety is connected essentially to mutational variety in the lipopolysaccharide (LPS) [10]. Phase I is the common stage found in tainted creatures, arthropods, or people. It is profoundly irresistible and compares to smooth LPS. Interestingly, phase II isn't exceptionally irresistible and is gotten uniquely in research centers after sequential sections in cell societies or embryonated egg cultures. It compares to rough LPS. Contrasted with phase I, phase II shows a shortened LPS and does not have a few protein cell surface determinants [11]. Hereditary inconstancy among various *C. burnetii* strains, as exhibited by various RFLP-based genomic groups, explicit plasmid regions, and LPS varieties, were probably identified with virulence. Genomic group I, II, and III were related with creature, tick, or intense Q fever human secludes, alluded to as intense strains, though group IV and V were related with human Q fever endocarditis separates, alluded to as persistent strains. Group VI segregates, gotten from wild rodents in Dugway (Utah), were of obscure pathogenicity. Examination of the different disconnects for LPS varieties, utilizing sodium dodecyl sulfate-polyacrylamide gel electrophoresis furthermore, immunoblotting, came about in segregates being put into bunches like the genomic bunches [12]. A few examinations recommend that inclining host factors are a higher priority than genomic strain variety in the clarification of the event of intense or persistent Q fever illnesses in people [13, 14].

Clinical Manifestation

In the majority of the cases, Clinical indications of Q fever are extremely mild or subclinical. The hatching period has been assessed to be roughly 20 days (range 14 to 39 days). No typical type of intense Q fever is exits. The clinical symptoms vary incredibly from patient to persistent. The most significant indicative sign is the epidemiological situation.

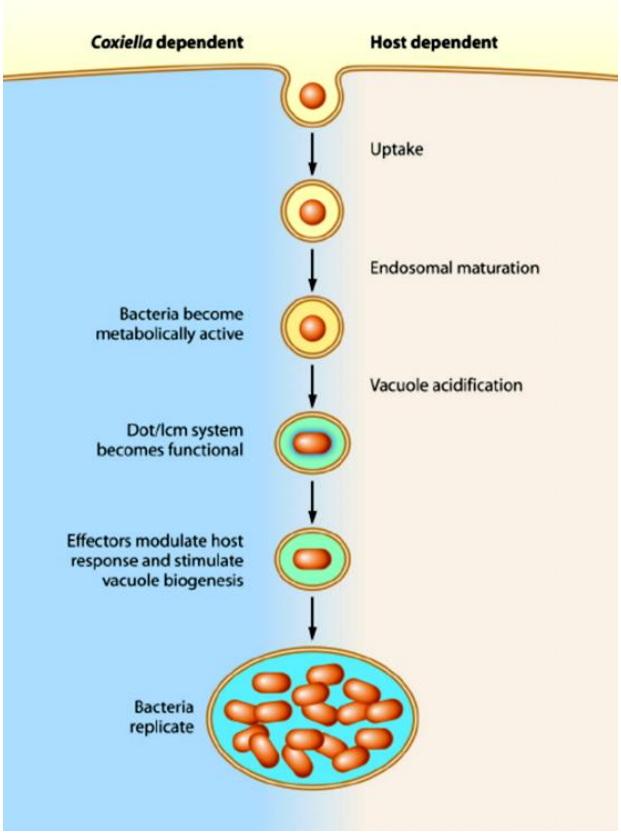

Figure 2: Pathogenesis of *C. burnetii* [33]

Ordinarily, three significant introductions are portrayed. These are as follows:-

Pneumonia - Atypical pneumonia is one of the most generally perceived types of intense Q fever. Most cases are clinically asymptomatic or gentle, described by an ineffective cough, fever, and insignificant auscultatory irregularities, yet a few patients present with intense respiratory misery. Pleural emission can likewise be available. Discoveries on the chest radiograph are vague. Marrie et al. [15] showed that 3.7% of all patients with community-acquired pneumonia admitted to a tertiary-care training clinic in Nova Scotia over a 5-year time span were expected to *C. burnetii*, which is like the discoveries of Lieberman et al. in Israel (5.8%) [16].

Self-limited influenza syndrome - A self-restricted influenza like condition is a very common sign of Q fever. In Spain, this type of Q fever has been shown as the reason for 21% of scenes of fever going on for over multi week and under 3 weeks. The most incessant indications, normally following an unexpected beginning, are high-grade fever (104°F or 40°C), fatigue, cerebral pain, and myalgias. The term of fever increments with increasing age.

Hepatitis (aggravation of the liver) – It is the dominating type of intense Q fever and it shows generally as a granulomatous hepatitis. The length of indications changes from 10 to 90 days. The death rate goes from 0.5 to 1.5%, contingent on the series [17]. Three significant types of hepatitis might be experienced: an irresistible hepatitis-like type of hepatitis with hepatomegaly however sometimes with jaundice, clinically asymptomatic hepatitis, and delayed fever of obscure origin with trademark granulomas on liver biopsy [18].

Other manifestations - Numerous other clinical appearances of intense Q fever is conceivable: myocarditis as well as pericarditis (which is often lethal), purpuric exanthema or maculopapular in 10% of patients [17], and extreme cerebral pain. Aseptic encephalitis and additionally meningitis, which happen in 0.2 to 1.3% of patients with Q fever [19], are once in a while joined by coma and seizures. Polyradiculoneuritis, hemolytic anemia, optic neuritis, thyroiditis, hemophagocytosis, transient hypoplastic anemia, gastroenteritis, pancreatitis, lymphadenopathy emulating lymphoma, erythema nodosum, bone marrow putrefaction, improper discharge of antidiuretic hormone, mesangioproliferative glomerulonephritis identified with antiphospholipid antibodies, and splenic burst are exceptional indications of intense Q fever [20].

Chronic infection:

Those Q fever which last over a half year after the onset, was initially depicted as chronic fever. Very few cases (roughly 5%) of *C. burnetii infection* experienced this type of fever and they may develop treacherously months to years after this

intense sickness. In the chronic form of Q fever, C. *burnetii* increase in macrophages and a perpetual rickettsemia brings about very elevated levels of steady antibodies. Basically, the primarily effecting organ is heart, and the other effecting organ may include liver, bone and arteries [21]. Patients having pre-existing valvular damage or the individuals who are immunocompromised usually experience endocarditis [22]. Chronic Q fever represents 3% of all instances of endocarditis in France, England and Lyon [23], and 15% in France, Marseille [24], and its yearly frequency is 0.75 cases per 1 million populaces in Israel [25]. In view of the absence of particularity of side effects, the disease analysis is sometimes delayed for 12 months to two years, bringing about an expanded death rate. Different indications of acute Q fever incorporate diseases of aneurysms or vascular unions [24], segregated hepatitis perhaps muddled by hepatic fibrosis furthermore, cirrhosis [21], and osteoarthritis and osteomyelitis [26]. Uncommon instances of pericardial emanation [27], aspiratory interstitial fibrosis, pseudotumor of the lung, lymphoma-like presentation, mixed cryoglobulinemia and amyloidosis have been reported in the literature.

Epidemiology

Method of Transmission -The vaporized route (inhalation of tainted fomites) is the essential method of contamination in human with C. *burnetii* (Figure 2) [28, 33]. Contamination by C. *burnetii* aerosol may happen directly from parturient liquids of tainted creatures, which may pollute placenta, infant creatures, or fleece [29]. C. *burnetii* is very impervious to slaughtering in nature and may survive for half a month in regions where creatures have been available; the bacterium may likewise be spread by the air [30, 31]. In this manner, Q fever may happen in patients who do not have any obvious contact with creatures. We have as of late contaminated amoebae with C. *burnetii* Nine Mile and showed that C. *burnetii* stayed feasible in amoebae for more than a month, as exhibited by the capacity to subculture microbes in HEL cells. In this manner, amoebae may view as a repository for C. *burnetii* in nature, as has been shown for Legionella species [32], and could represent a secured specialty in the wild.

Ingestion (mostly drinking crude milk) is considered as the minor route of transmission for C. *burnetii* infection [34, 35] and is presently even a state of contention. Individual person to-individual person transmission is likely incredibly uncommon. Albeit rare, irregular human Q fever cases have happened following contact with a tainted parturient lady (in an obstetrician who performed an abortion on the pregnant lady) through transplacental transmission bringing about inborn contaminations [36, 37], during examinations [38, 39], by means of intradermal immunization, or through blood transfusion. Despite the fact that C. *burnetii* has been disengaged from arthropods, predominantly ticks, arthropod-borne transmission of Q fever in people is probably not going to be significant [40, 41]. Notwithstanding, we have detailed two instances of coinfection with Rickettsia conorii and C. *burnetii* analyzed in patients living close Montpellier and suspect that they were brought about by a tick chomp. Sexual transmission of C. *burnetii* was illustrated tentatively in tainted mice [42]; notwithstanding, this method of transmission stays to be set up in people and wild creatures.

Reservoirs - Q fever is an overall zoonosis. The repositories are broad however just partially known and incorporate birds, warm blooded creatures, and arthropods, chiefly ticks. While a significant repository is seems to be little wild rodents, the most usually distinguished wellsprings of human disease are livestock, for example, goats, steers, and sheep. Pets, including dogs [43], cat, and rabbits, have likewise been shown to be possible wellsprings of metropolitan outbreaks. Cats are associated as a significant store with C. *burnetii* in metropolitan zones and might be the wellspring of metropolitan outbreaks [44-46]. In Canada, 6 to 20% of felines have anti- C. *burnetii* antibodies [47]. Wild rodents have been suspected as a significant store in Great Britain [48]. All these vertebrates, when contaminated, shed the parching safe organisms in milk, dung, pee, and, particularly, birth items [49]. Reactivation of disease happens in female vertebrates during pregnancy. Q fever causes abortions in goats and, less often, sheep and causes conceptive issues in steers [50]. High groupings of C. *burnetii* (up to 109 microorganisms for every g of tissue) are found in the placentas of tainted creatures. Because of its protection from physical agents, presumably identified with its sporulation cycle [49], *C. burnetii* remain active for extensive stretches in the climate.

Geographic Distribution - In Europe, intense Q fever cases are all the more much of the time revealed in spring and late-spring. They may happen at all ages; however, they are less frequent in ladies than in men. Q fever is normally benevolent; however, mortality happens in 1 to 11% of patients with persistent Q fever [51]. *C. burnetii* is endemic in all over the world aside from New Zealand [52]. Since the clinical introduction is extremely pleomorphic furthermore, vague, the frequency of Q fever among people is most likely belittled, and determination especially depends upon the doctor's familiarity with the side effects of Q fever furthermore, the presence of a reliable research facility. In southern France, 5 to 8% of instances of endocarditis are occurs due to *C. burnetii*, and the commonness of intense Q fever is 50 cases per 100,000 occupants [19]. Seroepidemiological studies have demonstrated that 18.3% of blood givers in Morocco, 37% in Zimbabwe [54], 26% in Tunisia [53], 44% in Nigeria [55], 14.6 to 36.6% in various territories of Canada and 10 to 37% in upper east Africa had hostile to C. *burnetii* antibodies. Huge flare-ups of Q fever have additionally been accounted for in Switzerland [57], in the Basque country in Spain [56], in Great Britain [58], and in Germany, Berlin [59].

Also, countless Q fever cases have been found in The Netherlands since 2007, with more than 3700 human cases announced through March 2010. Tainted dairy goat ranches are accepted to be the wellspring of the outbreaks, and most human cases have been found in the southern locale of the country [60].

Laboratory Diagnosis

Collection and Handling of Clinical Specimens

Clinical materials, which are collected from patients probably tainted with C. *burnetii* ought to be tackled very carefully by experienced staff wearing masks and gloves and specifically in the laboratories which have biosafety level 3 research facilities. The same measures should be applied while handling *C. burnetii* -contaminated cell cultures or *C. burnetii* -tainted creatures. Vaccination may consider as significant for those

personnel of research laboratory who work with *C. burnetii* - contaminated creatures.

Pathological Findings and Immunohistology

Immunodetection procedures might be use to distinguish the organs which are affected by *C. burnetii*. Immunodetection might be performed by catch ELISA/ELIFA systems [59], immunoperoxidase strategy [62], monoclonal antibodies [63, 61] or immunofluorescence with polyclonal. Only the monoclonal antibody strategy might be utilized with paraffin inserted tissues. Brouqui et al. [62] utilized an immunohistochemical procedure to examine valve specimens from 17 Q fever endocarditis patients. They found that in contaminated heart valves, C. *burnetii* was noticeable as a voluminous intracytoplasmic mass inside tainted mononuclear cells and not extracellularly concerning most other etiological operators of infective endocarditis. Intracellular duplication of C. *burnetii* may clarify why heart valve vegetations are little or nonexistent in Q fever endocarditis patients and in this manner are frequently not imagined by echocardiography.

DNA Probes and DNA Amplification - Radiolabeled DNA probes were first utilized for identification and detection of C. *burnetii* strains [64-66] from culture or clinical sample. All the more as of late, C. *burnetii* DNA enhancement from clinical sample by PCR has been utilized effectively [67]. The method may permit the evaluation of C. *burnetii* in tissue tests. All the more as of late, an open perusing outline encoding a polypeptide of 367 amino acids was discovered downstream of the heat shock proteins qualities (htpAB qualities) [68]. Primers obtain from htpAB-related arrangement were utilized in a PCR examine for recognition of C. *burnetii* in bovine's milk [70]. The presence of different duplicates of the target sequence in C. *burnetii* genome may build the affectability of this PCR assay. PCR-based methods are likewise used to identify C. *burnetii* DNA inside contaminated societies in shell vial supernatants [69]. By utilizing this procedure, positive blood cultures were recognized in 9 of 17 Q fever endocarditis patients (53%) and 11 of 66 Q fever pneumonia patients (17%) when blood samples were gathered before inception of the antibiotic treatment [69].

Serology - Q fever analysis stays dependent on serological strategies since molecular biology methods and cultures have low affectability and are accessible only in reference research centers. Serological analysis is not that much difficult to build up, in spite of that antibodies are generally recognized almost after a month from the beginning of the sickness. In this way, serological tests ought to be performed on both intense and recuperating stage sera. In addition, serology permits the separation of intense and constant Q fever contaminations. Strategies which have been utilized incorporate supplement obsession [72, 73], radioimmunoassay [71], microagglutination [74, 75], IFA [75, 72], ELISA [77, 78], aberrant hemolysis test [79], chemical connected immunosorbent fluorescence measure (ELIFA) [80], Western smudging [81, 82] and spot immunoblotting. The methods most ordinarily utilized incorporate supplement obsession, ELISA, IFA, also, microagglutination. Just the initial two strategies are accessible commercially.

Prevention - In USA, some occupations termed as "In danger" for becoming more susceptible to Q fever outbreaks, which incorporate: animal transporters, stockyard workers, veterinary personnel, shearers, farmers, laboratory workers, and people who cull. Prevention and control endeavors ought to be coordinated essentially toward these environments and groups [83].

The accompanying measures ought to be utilized in the counteraction and control of Q fever - [84-86]

1. Educate the general population about the possible wellsprings of contamination.
2. Vaccinate people occupied with research dealing with pregnant sheep or live *C. burnetii*.
3. Appropriately discard Placenta, fetal films, birth items, and aborted fetuses at facilities housing goats and sheep.
4. Only pasteurized dairy items and milk should be use.
5. Restrict admittance to horse shelters and research laboratories utilized in housing conceivably tainted creatures.
6. Quarantine imported creatures.
7. For autoclaving, packing, furthermore, washing of research laboratory dress some high specific and appropriate methods must be used.
8. Ensure that holding offices for sheep ought to be found away from populated zones. Creatures ought to be regularly tried for antibodies to *C. burnetii*, and measures ought to be executed to forestall airflow to other involved territories.

Standard Therapies

Doxycycline is most commonly used as a treatment for kids and adults with extreme sickness. After Q fever suspicions, treatment must be introduced as quickly as possible. Utilization of other class of antibiotics except doxycycline or variety of tetracyclines is related with a higher danger of serious sickness. Subsequently, treatment must be founded on clinical suspicions alone and ought to consistently start before lab results return. In the event that the patient is treated within the initial 3 days of the infection, fever by and large dies down inside 72 hours. Actually, inability to react to doxycycline proposes that the patient's illness probably not related with Q fever.

For treatment of Q fever in children doxycycline is preferred over tetracyclines because they don’t show any interaction with dairy products or leave any permanent strain on patient’s teeth like tetracyclines. Children who are younger 8 years might be treated with co-trimoxazole in case of mild illness, yet treatment ought to be changed to doxycycline if severity of their illness increased.

Substitute medicine might be use for treatment of patients having dangerous hypersensitivities to doxycycline and in case of pregnant patients. Treatment of pregnant ladies identified to have intense Q fever with co-trimoxazole all through pregnancy has been appeared to remarkably diminish the danger of unfavorable ramifications for the baby [3].

Investigational Therapies

Fluoroquinolones, which are anti-infection agents that eliminate microorganisms or forestall their development (antimicrobials), have likewise been utilized to treat people with Q fever. These medications incorporate ofloxacin,

pefloxacin, and ciprofloxacin. Extra anti-microbials that have been utilized to treat people with Q fever incorporate chloramphenicol, co-trimoxazole and rifampin. More exploration is important to decide the drawn-out security and viability of these possible treatments.

Macrolides are a class of anti-microbials that have been utilized to treat people with Q fever. A typical macrolide is erythromycin. Nonetheless, macrolides have commonly been untrustworthy. More current macrolides, for example, clarithromycin, azithromycin and roxithromycin have indicated more prominent guarantee as expected treatments for Q fever. More examination is important to decide the drawn-out security and viability of fresher macrolides as expected medicines for people with Q fever.

Discussion

Chronic Q fever endocarditis might be related with an atypical introduction and have an extended course disregarding antibiotic treatment. Serological reaction in persistent Q fever might be related with a low or fluctuating neutralizer titre. The chance of constant Q fever should be considered as a reason for an unexplained fever and ought not to be excused within the sight of a lacking or atypical serological reaction, particularly in immunosuppressed patients. Cautious clinical and serological development is fundamental in high-hazard patients to identify its advancement over the long run. More exploration is expected to improve research center finding, including reexamination of the suggested serological standards for the identification of Q fever endocarditis.

Conflict of interest: The authors proclaim no conflict of interest.

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