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Brucellosis Beyond the Acute Phase: Distinguishing Relapse, Persistent Infection, Focal Disease, Residual Sequelae, and Postinfectious Symptoms

Akut Evre Sonrası Bruselloz: Nüks, Kalıcı Enfeksiyon, Fokal Hastalık, Rezidüel Sekeller ve Enfeksiyon Sonrası Semptomların Ayırt Edilmesi

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Abstract

Brucellosis can produce prolonged consequences, but terminology for postacute manifestations remains inconsistent. This narrative review distinguishes relapse, persistent infection, focal disease, residual sequelae, and postinfectious symptoms. PubMed, Scopus, and Google Scholar were searched for studies published from 2016 to 2026. Although intracellular persistence mechanisms are well established, they do not fully explain prolonged symptoms in humans. Combination antibacterial therapy is the standard treatment; persistent symptoms require reassessment for relapse or sequelae. Evidence supporting brucellosis-specific rehabilitation remains limited. Routine rehabilitation pathways are not supported; individualized supportive rehabilitation should be considered only for selected patients with measurable neurologic or osteoarticular impairments. Prospective studies using clearly defined phenotypes are needed.

Keywords: Brucellosis, recurrence, persistent infection, rehabilitation, quality of life

Öz

Bruselloz uzun süreli sonuçlara yol açar, ancak akut evre sonrasına ilişkin terminoloji tutarsızlığını korumaktadır. Bu derleme; nüks, kalıcı enfeksiyon, fokal hastalık, rezidüel sekeller ve enfeksiyon sonrası semptomları birbirinden ayırmaktadır. PubMed, Scopus ve Google Scholar (2016–2026) veritabanları taranmıştır. Hücre içi kalıcılık mekanizmaları iyi bilinmekle birlikte, bunlar insanlarda görülen uzun süreli semptomları tam olarak açıklayamamaktadır. Kombine antibakteriyel tedavi standart yaklaşımdır; kalıcı semptomların varlığında nüks veya sekeller açısından yeniden değerlendirme yapılması gerekir. Bruselloza özgü rehabilitasyon uygulamalarına dair kanıtlar sınırlıdır. Rutin rehabilitasyon süreçleri desteklenmemektedir; kişiselleştirilmiş destekleyici rehabilitasyon, ölçülebilir nörolojik veya osteoartiküler bozuklukları olan seçilmiş hastalar için düşünülmelidir. Belirgin fenotiplerin kullanıldığı prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Bruselloz, nüks, kalıcı enfeksiyon, rehabilitasyon, yaşam kalitesi

Introduction

Brucellosis remains an important bacterial zoonosis in many endemic regions and poses substantial diagnostic, therapeutic, and public health challenges[1-5]. Its clinical spectrum ranges from acute systemic febrile illness to focal involvement of the osteoarticular, neurologic, cardiovascular, genitourinary, and other organ systems. Underdiagnosis, delayed diagnosis, and the requirement for prolonged combination antibacterial therapy further contribute to the overall burden of disease[1,3,6,7].

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A major challenge in the literature is the inconsistent use of the term chronic brucellosis. Historical studies and regional clinical practices have applied this label according to variable duration-based, symptom-based, serologic, or locally defined criteria. However, major contemporary international guidance does not endorse a universally accepted duration-based definition, and symptom duration alone cannot reliably distinguish ongoing infection from relapse, focal disease, reinfection, residual organ damage, or postinfectious symptoms[1,6,8-10]. Accordingly, this review does not apply a duration threshold as a diagnostic criterion and does not consider chronicity to represent a single clinical entity. The term chronic brucellosis is used only when referring to terminology adopted in an original study or when discussing the historical literature.

For conceptual clarity, this review distinguishes five clinically relevant categories: (i) microbiologically or clinically suspected persistent infection, (ii) relapse following an initial response to therapy, with reinfection considered separately in endemic settings, (iii) focal brucellosis involving a defined organ system, (iv) residual structural or neurologic sequelae following treated infection, and (v) postinfectious or non-specific persistent symptoms, including fatigue, pain, sleep disturbance, and reduced quality of life in the absence of sufficient evidence of active infection (Table 1). This distinction is clinically important because these categories differ in their diagnostic evaluation, underlying pathophysiology, treatment implications, and potential requirements for rehabilitation.

The aim of this narrative review is therefore to synthesize contemporary evidence on brucellosis beyond the acute phase by explicitly distinguishing these clinical entities, examining what experimental evidence on intracellular persistence can and cannot explain about human disease, and critically appraising the limited evidence regarding functional assessment and rehabilitation.

Literature Review Strategy

This article is a narrative review. The core search covered publications from January 1, 2016, through August 31, 2026, in PubMed and Scopus. Google Scholar was not treated as an exhaustive primary database; rather, it was used for supplementary citation tracking, identification of region-specific literature, and retrieval of reports identified through database or reference-list searches. Candidate records identified through Google Scholar were included only after their relevance was confirmed from the abstract or full text and their bibliographic details were verified against an indexed database or publisher source. Official documents from the World Health Organization (WHO), the United States Centers for Disease Control and Prevention, and the European Centre for Disease Prevention and Control were also reviewed. Seminal studies published before 2016 were deliberately included when they provided foundational evidence on *Brucella*-containing vacuole (BCV) biology, VirB-dependent type IV secretion, intracellular trafficking, molecular persistence after treatment, or region-specific epidemiology that remained directly relevant to the review question.

The PubMed search combined disease-related terms with concepts related to relapse, persistence, focal disease, sequelae, fatigue, functional outcomes, quality of life, rehabilitation, and intracellular survival. The principal search syntax was ("Brucellosis"[MeSH Terms] OR brucellosis[Title/Abstract] OR *Brucella*[Title/Abstract]) AND (relapse*[Title/Abstract] OR recurrent*[Title/Abstract] OR persist*[Title/Abstract] OR "Persistent Infection"[MeSH Terms] OR focal[Title/Abstract] OR sequela*[Title/Abstract] OR "post-brucellosis"[Title/Abstract]

Table 1. Operational terminology used in this review.

Term	Operational use in this review	What it should not be assumed to mean
Relapse	Recurrence of compatible disease after an initial therapeutic response; interpretation should consider treatment adherence, microbiological or serological evidence, focal disease, and timing.	Any recurrent non-specific symptom or reinfection following new exposure.
Reinfection	A new episode following renewed exposure in an endemic setting when epidemiological and clinical evidence supports a new infection.	Relapse by default.
Persistent infection	Ongoing infection considered clinically or biologically plausible and supported by appropriate evidence.	Persistent seropositivity or PCR-detected DNA alone, or symptom duration alone.
Focal disease	Organ-specific brucellosis, such as spondylitis, sacroiliitis, neurobrucellosis, or endocarditis.	A generic synonym for chronic brucellosis.
Residual sequelae	Persistent structural, neurologic, pain-related, or functional consequences after treatment of the infection.	Evidence of ongoing bacterial replication.
Postinfectious symptoms	Persistent fatigue, pain, sleep disturbance, or reduced well-being without sufficient evidence of active infection.	A single defined post-brucellosis syndrome or an indication for additional antibiotics.

PCR, polymerase chain reaction.

OR fatigue[Title/Abstract] OR rehabilitation[Title/Abstract] OR disability[Title/Abstract] OR "quality of life"[Title/Abstract] OR VirB[Title/Abstract] OR "type IV secretion"[Title/Abstract] OR "*Brucella*-containing vacuole"[Title/Abstract]). The search syntax was adapted for Scopus using TITLE-ABS-KEY terms. The search concepts and the role of each source are summarized in Table 2.

Eligible publications included systematic reviews, meta-analyses, cohort and case-control studies, clinically relevant observational studies, contemporary narrative reviews, and guidance documents addressing human brucellosis epidemiology, diagnosis, relapse, focal complications, treatment, long-term symptoms, quality of life, or rehabilitation. Experimental cell and animal studies were included only in the mechanistic section addressing intracellular survival and were not considered direct evidence of chronic clinical syndromes in humans. Duplicate records, publications lacking direct relevance to the review objectives, and purely veterinary studies without mechanistic relevance to human infection were excluded. The core clinical synthesis prioritized full-text publications in English; non-English, disease-specific rehabilitation reports were considered when an indexed English abstract and a verifiable bibliographic record were available.

Because this was a narrative rather than a systematic review, no formal risk-of-bias assessment tool or quantitative certainty-grading framework was applied. Evidence was appraised qualitatively according to study design, population, disease specificity, outcome directness, and consistency with other studies. More recent clinical evidence was prioritized when it addressed the same question as older studies, whereas older studies were retained when they were seminal, uniquely informative, or necessary to explain the historical evolution of relevant concepts.

Epidemiological Context and Transmission

Human brucellosis remains concentrated in regions where infection persists among livestock and occupational or foodborne exposure continues. The Mediterranean basin, the Middle East, parts of Africa and Latin America, and Central Asia remain important endemic settings, although surveillance intensity and case ascertainment vary considerably across countries[2-5,11]. The principal routes of human infection include consumption of unpasteurized dairy products, direct occupational contact with infected animals or animal tissues, and laboratory or other aerosol exposure[1,3,5].

Central Asia is considered here as an illustrative endemic setting rather than the exclusive geographic focus of this review. In Samarqand Oblast, Uzbekistan, a matched case-control study involving 144 patients and 288 controls identified direct livestock-related and food-related exposures as important risk factors for human brucellosis, providing country-specific evidence for the importance of prevention at the human-animal interface[12]. Similar One Health principles apply across endemic regions; however, the intensity and relative contribution of individual risk factors should be interpreted in the context of local epidemiological data rather than generalized assumptions about socioeconomic conditions or dietary behaviors[5].

Clarifying "Chronicity": Distinct Clinical Entities

The clinical literature has used the term chronic brucellosis inconsistently. Some older or regional studies defined it according to symptom duration, serologic persistence, recurrent complaints, or locally established clinical criteria, whereas contemporary international sources more commonly describe relapse, focal complications, treatment failure, reinfection, or persistent symptoms without establishing a single duration-based category of chronic disease[1,6,8-10]. This heterogeneity limits comparability across studies and may lead to the inappropriate inference that persistent symptoms necessarily indicate ongoing viable infection.

Relapse refers to the recurrence of compatible clinical disease after an initial response to adequate treatment, ideally supported by renewed microbiological or serological evidence and interpreted in the context of treatment adherence, the

Table 2. Literature search sources and their role in the narrative review.

Source	Search approach/role
PubMed	Core database; MeSH and title/abstract terms for brucellosis were combined with concepts related to relapse, recurrence, persistence, focal disease, sequelae, fatigue, rehabilitation, disability, quality of life, VirB, type IV secretion, and BCV.
Scopus	Core database; analogous TITLE-ABS-KEY concepts adapted to Scopus syntax.
Google Scholar	Supplementary source for citation tracking and identification of regional or difficult-to-index literature; candidate sources were verified before inclusion.
WHO/CDC/ECDC	Sources for official definitions, epidemiological context, public health guidance, and general rehabilitation frameworks.
Backward citation searching	Used to identify seminal pre-2016 mechanistic and persistence studies that were retained when uniquely relevant to BCV/VirB biology, molecular persistence, or regional epidemiology.

MeSH, Medical Subject Headings; BCV, *Brucella-containing* vacuole; WHO, World Health Organization; CDC, United States Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control.

therapeutic regimen, and the presence of focal infection. Reinfection represents a separate possibility in endemic areas where ongoing exposure continues. Recent cohort studies underscore that estimates of relapse are strongly influenced by the case definition used and by whether incomplete treatment, re-exposure, and alternative diagnoses are appropriately excluded[9,10].

Persistent infection should be reserved for situations in which ongoing infection remains biologically or clinically plausible and is supported by appropriate evidence. Molecular detection after treatment requires particular caution. *Brucella* DNA has been detected for prolonged periods after apparent clinical cure, including in asymptomatic individuals, and persistent DNA levels have not consistently distinguished patients who subsequently relapse[13,14]. Therefore, detection of bacterial DNA should not automatically be equated with the presence of viable organisms or active disease.

Focal disease denotes organ-specific involvement, such as spondylitis, sacroiliitis, neurobrucellosis, or endocarditis. Focal disease may occur during the initial infection or become apparent later and has specific diagnostic and therapeutic implications. By contrast, residual sequelae represent persistent structural or functional consequences after the infection has been treated, whereas postinfectious symptoms encompass fatigue, pain, sleep disturbance, or reduced well-being in the absence of sufficient evidence of active focal or systemic infection. These distinctions are applied throughout the remainder of this review.

Biological Basis of Intracellular Persistence: What Experimental Evidence Shows

Brucella species are facultative intracellular pathogens whose ability to survive within professional phagocytes is central to their virulence. Experimental studies have shown that intracellular *Brucella* remodels its vacuolar compartment, traffics through endosomal compartments, and establishes a replication-permissive niche associated with the endoplasmic reticulum. The VirB type IV secretion system is essential for this intracellular trafficking and replicative program in established cellular and animal models[15-19]. Seminal studies demonstrated that disruption of virB impairs BCV maturation, promotes lysosomal degradation, and prevents formation of the intracellular replication niche[15,16]. Subsequent studies demonstrated dependence on host secretory trafficking and a defined late endosomal/lysosomal transit pathway before intracellular replication[17,18].

These experiments provide strong biological evidence for mechanisms that facilitate intracellular survival and persistence. However, they do not establish that a single BCV/VirB pathway directly accounts for the heterogeneous clinical syndrome historically termed chronic human brucellosis. Extrapolating from cellular or animal models of persistence to prolonged human symptoms requires additional clinical evidence, particularly because relapse, focal infection, residual tissue injury, and postinfectious symptoms can produce superficially similar clinical presentations.

Human immunologic studies also support complex host-pathogen interactions. Reviews have described modulation of Toll-like receptor signaling, antigen presentation, cytokine responses, and other immune pathways during *Brucella* infection[20,21]. Hou et al.[22] reported changes in myeloid-derived suppressor cells in a population classified by the investigators as having chronic brucellosis. Although this finding is relevant to immune regulation, the study-specific definition should not be generalized as an internationally accepted diagnostic category. Overall, intracellular survival and immunomodulation provide biological plausibility for persistence; however, their direct contributions to specific long-term human phenotypes remain incompletely defined.

Relapse, Persistent Infection, and Focal Disease

Relapse is a clinically important outcome after treatment for brucellosis, but reported rates vary according to treatment regimen, adherence, duration of follow-up, ongoing exposure, and case definition. Recent cohort studies from endemic regions have emphasized the need to distinguish true relapse from incomplete treatment, reinfection, and alternative explanations for recurrent symptoms[9,10]. This distinction is particularly important when serologic titers remain positive after treatment or when non-specific symptoms recur without objective evidence of active disease.

Focal complications are among the strongest predictors of prolonged morbidity. Osteoarticular disease includes peripheral arthritis, sacroiliitis, spondylitis/spondylodiscitis, bursitis, and tenosynovitis. *Brucella* spondylitis is particularly important because pain, impaired mobility, abscess formation, neurologic compression, and the need for prolonged treatment can result in persistent functional impairment[23]. Neurobrucellosis is less common but clinically heterogeneous; meningitis, encephalitis, cranial neuropathies, radiculopathy, myelopathy, and hearing impairment have all been described, and some patients experience persistent neurologic deficits after microbiological treatment[24].

The diagnostic approach to prolonged or recurrent symptoms should therefore be phenotype-based. New fever, objective inflammatory findings, focal pain accompanied by compatible imaging abnormalities, neurologic deficits, new culture or molecular evidence, and a relevant treatment or exposure history should prompt evaluation for active relapse or focal disease. In contrast, fatigue or pain alone after adequate

therapy does not establish active infection and warrants broader clinical assessment.

Post-treatment Symptoms, Residual Sequelae, and Functional Outcomes

Persistent fatigue, pain, sleep disturbance, emotional distress, and reduced activity have been reported following brucellosis, but these manifestations should not be equated with persistent infection. They may reflect residual osteoarticular or neurologic injury, prolonged deconditioning, pain-related disability, comorbid conditions, psychological responses to chronic illness, or a non-specific postinfectious state. Accordingly, the revised terminology replaces the term persistent asthenic syndrome with persistent fatigue or postinfectious fatigue when active infection has not been demonstrated.

Quality-of-life studies provide evidence that brucellosis can affect patients beyond traditional microbiological and biochemical outcomes. A case-control study from Herat, Afghanistan, using the 36-Item Short Form Health Survey (SF-36), documented impairment across physical and mental health domains among patients with brucellosis[25]. These findings support systematic assessment of functioning and quality of life; however, they do not establish that all patients with persistent symptoms require formal rehabilitation or that such symptoms result from ongoing bacterial persistence.

The most defensible disease-specific indication for functional follow-up is the presence of measurable impairment, including persistent limitations in mobility or activities following osteoarticular disease, residual neurologic deficits, chronic pain associated with activity restriction, or substantial deconditioning after severe or prolonged illness. The intensity and duration of follow-up should therefore be individualized according to the clinical phenotype rather than determined by a single calendar-based definition of chronicity.

Antibacterial Therapy, Relapse, and Antimicrobial Resistance

Antibacterial therapy remains the cornerstone of evidence-based treatment for active brucellosis. Because *Brucella* is an intracellular pathogen and monotherapy is associated with treatment failure and relapse, combination regimens are standard. Comparative evidence indicates that regimen selection and treatment duration influence relapse risk and that focal disease, particularly spondylitis and neurobrucellosis, may require prolonged and individualized therapy[1,6,23,24,26].

Antimicrobial resistance in *Brucella* has been reported inconsistently across settings. A systematic review and meta-analysis described geographic variation in susceptibility to agents including rifampicin and co-trimoxazole[27]. These findings support continued attention to emerging resistance and consideration of local susceptibility data when reliable testing is available. However, current international guidance does not establish routine local antimicrobial resistance surveillance as a mandatory component of brucellosis management in every endemic setting; it is more appropriately regarded as a potential public health and research priority rather than a universal clinical recommendation.

Persistent symptoms after antibacterial treatment should not automatically prompt additional courses of antimicrobial therapy. Reassessment should first distinguish relapse or focal disease from reinfection, residual tissue damage, medication-related effects, unrelated comorbidities, and postinfectious symptoms. Repeated or prolonged antibiotic treatment without objective evidence of active infection may expose patients to unnecessary adverse effects while delaying identification of the actual cause of persistent symptoms.

Rehabilitation: Current Evidence and Its Limitations

Rehabilitation is an important general health intervention for individuals with functional limitations, and WHO frameworks emphasize functioning, activity, participation, and person-centered rehabilitation across health conditions[28-30]. However, these WHO documents are not brucellosis-specific guidelines. They should therefore be interpreted as conceptual health-system frameworks rather than as evidence that routine rehabilitation is required for all patients with brucellosis.

Brucellosis-specific evidence on rehabilitation remains sparse. A clinical study involving patients described as having residual brucellosis with musculoskeletal involvement reported improvements in quality-of-life and psychosomatic outcomes following non-pharmacological treatment complexes[31]. This finding provides disease-specific evidence that selected patients with residual musculoskeletal impairment may benefit from rehabilitative interventions; however, the study setting, population, terminology, and multimodal intervention package limit its generalizability. The available evidence is insufficient to recommend a uniform multidisciplinary pathway for all patients or to prescribe rehabilitation alongside antimicrobial therapy as a standard disease-specific intervention.

A cautious, evidence-based position is that rehabilitation may be considered for selected patients with objective or patient-important functional impairment after active infection has been appropriately assessed and treated. Potential indications include persistent mobility limitations after spondylitis or sacroiliitis, residual neurologic deficits, chronic pain associated with activity restriction, impaired endurance following severe illness, or difficulty returning to usual roles. Interventions should target the predominant impairment and may include graded therapeutic exercise, mobility and strengthening exercises, pain-management strategies, education, and psychological support when clinically indicated. The specific

intervention plan should be individualized and coordinated with ongoing assessment for active focal disease.

Functional Outcome Measures: Potential Use Rather Than Disease-Specific Validation

The International Classification of Functioning, Disability, and Health (ICF) provides a general conceptual framework for describing body functions and structures, activity, participation, and contextual factors[28]. The WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) is a generic measure of disability that is conceptually linked to the ICF[30]. Neither instrument has been specifically validated or established as a mandatory outcome measure for brucellosis.

SF-36 has been used in brucellosis-specific quality-of-life research and can provide information on physical and mental health domains[25]. The visual analog scale (VAS) is a generic measure of pain intensity, whereas the six-minute walk test (6MWT) is a generic measure of functional exercise capacity[32,33]. Accordingly, their use in brucellosis is best regarded as an extrapolation from general rehabilitation practice, with the exception of the SF-36, which has direct precedent in brucellosis studies. Table 3 summarizes the evidentiary status of these measures.

No brucellosis-specific evidence supports mandatory use of the WHODAS 2.0, SF-36, VAS, or 6MWT in every patient, and no high-quality disease-specific evidence establishes fixed reassessment intervals, such as 4–6 weeks, 3 months, or 6–12 months. Assessment tools and follow-up timing should instead be selected according to the predominant impairment, clinical course, treatment phase, and purpose of follow-up.

Authors' Conceptual Clinical Framework

On the basis of the reviewed evidence, we propose a conceptual, rather than guideline-based, framework for patients who remain symptomatic after treatment for brucellosis. Its primary purpose is to prevent persistent symptoms from being conflated with active infection. First, clinicians should reassess for relapse, reinfection, treatment non-adherence, and focal disease on the basis of the symptom pattern, exposure history, physical examination, inflammatory markers, microbiological findings, and targeted imaging when indicated. Second, when active infection is not demonstrated, residual structural or neurologic sequelae and non-infectious causes of symptoms should be evaluated. Third, patients with measurable limitations in mobility, pain-related activity, endurance, neurologic function, or participation may be referred for individualized supportive rehabilitation. Generic functional measures may be selected to establish a relevant baseline and document change over time; however, no specific instrument or reassessment schedule is proposed as mandatory (Table 4).

This framework is informed by general WHO rehabilitation principles, disease-specific observations concerning focal complications and quality of life, and the limited literature on brucellosis rehabilitation. It should be regarded as a hypothesis-generating clinical organization of the available evidence rather than as a disease-specific WHO recommendation or an established standard of care.

Areas of Uncertainty and Research Priorities

Several important questions remain unresolved. First, human studies require standardized definitions that clearly distinguish relapse, reinfection, persistent infection, focal disease, residual sequelae, and postinfectious symptoms. Second, longitudinal studies integrating microbiological, imaging, inflammatory, immunologic, and functional outcomes are needed to determine whether any biomarkers can reliably distinguish active persistent infection from post-treatment symptoms. Third, mechanistic discoveries involving BCV biology, VirB effectors, and immune regulation require careful translation into clinically defined human phenotypes rather than an assumption of a single pathway underlying chronicity. Finally,

Table 3. Functional frameworks and outcome measures discussed in the review.

Measure/ framework	What it measures	Brucellosis-specific evidentiary status
ICF	Conceptual framework for describing functioning, activity, participation, and contextual factors.	Generic WHO framework; not a brucellosis-specific guideline.
WHODAS 2.0	Generic disability and functioning.	Generic instrument; no brucellosis-specific validation has been identified to support routine mandatory use.
SF-36	Health-related quality of life.	Directly used in brucellosis-specific quality-of-life research but not established as a standard mandatory outcome measure.
VAS	Pain intensity.	Generic pain measure; its application to brucellosis is extrapolated from general clinical practice.
6MWT	Functional exercise capacity and endurance.	Generic functional test; no brucellosis-specific validation has been identified to support routine use.

ICF, International Classification of Functioning, Disability, and Health; WHODAS 2.0, WHO Disability Assessment Schedule 2.0; SF-36, 36-Item Short Form Health Survey; VAS, visual analog scale; 6MWT, six-minute walk test.

Table 4. Authors' conceptual framework for persistent symptoms after brucellosis treatment (not a guideline).

Step	Clinical question	Possible action
1. Reassess active disease	Is there evidence for relapse, reinfection, treatment failure, or focal brucellosis?	Review exposure/adherence; targeted examination, inflammatory markers, microbiology, and imaging as clinically indicated.
2. Characterize sequelae	If active infection is not demonstrated, is there residual structural, neurological, pain-related, or other pathology?	Targeted specialty assessment and management of the identified sequela.
3. Assess functioning	Is there measurable limitation in mobility, endurance, daily activity, participation, or quality of life?	Select a relevant generic measure when it will inform care or document change; no mandatory battery.
4. Consider rehabilitation	Would target rehabilitation address a defined impairment?	Individualized supportive rehabilitation for selected patients; coordination with management of focal disease and comorbidity.
5. Reassess	Is the clinical course improving, stable, or worsening?	Individualize timing according to phenotype and treatment phase; no fixed disease-specific interval is established.

controlled, brucellosis-specific rehabilitation studies are needed to define appropriate patient selection, intervention components, safety, timing, and clinically meaningful outcomes.

Conclusion

Current evidence does not support a single duration-based definition of chronic brucellosis. Relapse or reinfection, persistent infection, focal organ disease, residual structural or neurologic sequelae, and nonspecific postinfectious symptoms have distinct evidentiary and therapeutic implications. Experimental studies of BCV maturation, VirB-dependent type IV secretion, and immunomodulation elucidate important mechanisms underlying intracellular survival, but they do not, by themselves, establish a unified mechanism for prolonged clinical disease in humans. Combination antibacterial therapy remains the cornerstone of active infection management, whereas recurrent or persistent symptoms require renewed diagnostic phenotyping rather than automatic attribution to ongoing infection. Long-term functional burden is best documented in focal osteoarticular and neurologic disease and in quality-of-life studies. Brucellosis-specific evidence supporting rehabilitation remains limited; individualized rehabilitation may be appropriate for selected patients with measurable impairment, whereas routine pathways, fixed reassessment intervals, and mandatory generic outcome batteries require prospective validation.

Footnotes

Authorship Contributions

Concept: N.T.R., R.N.R., Design: N.T.R., R.N.R., Data Collection or Processing: N.A.Y., R.N.R., Analysis or Interpretation: N.T.R., Literature Search: N.A.Y., R.N.R., Writing: N.A.Y., R.N.R.

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