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Multisystemic Challenges and Multidisciplinary Management of Behcet's Disease: Integrating Precision Diagnosis, Targeted Therapy, and Functional Rehabilitation

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ABSTRACT

***Background*:** Behcet'sdisease (BD) is a chronic, relapsing, multisystem inflammatory vasculitis with variable vessel involvement, presenting a broad spectrum of manifestations across mucocutaneous, ocular, vascular, neurological, gastrointestinal, and musculoskeletal systems. The heterogeneity of its clinical expression, unpredictable course, and lack of disease-specific biomarkers pose persistent challenges for timely diagnosis, individualized treatment, and prevention of irreversible organ damage. Rheumatologists frequently serve as primary coordinators of BD care, given their expertise in systemic inflammatory disease, yet optimal outcomes often require close collaboration with ophthalmologists, neurologists, vascular surgeons, dermatologists, gastroenterologists, and rehabilitation specialists. Diagnostic complexity arises from overlapping features with other vasculitides and autoimmune diseases, geographic variation in disease patterns, and the relapsing-remitting nature of symptoms. Advances in imaging, such as high-resolion doppler ultrasound, magnetic resonance (MR) angiography, and optical coherence tomography for ocular monitoring, have enhanced early detection of organ involvement. Novel biomarkers, including circulating endothelial cells, neutrophil extracellular trap (NET) components, and cytokine signatures, hold promise for improving diagnostic specificity and prognostication. Management strategies must be tailored to disease phenotype and severity. Mucocutaneous and articular manifestations often respond to colchicine and conventional immunosuppressants, whereas major organ involvement typically necessitates targeted biologics, including anti-tumor necrosis factor(TNF) agents, interleukin (IL)-1 inhibitors, and IL-6 receptor antagonists. Rheumatologists play a pivotal role in risk stratification, treatment sequencing, and balancing immunosuppression with vascular safety considerations. Multidisciplinary care models facilitate integrated monitoring, especially for complex cases such as ocular BD requiring rapid ophthalmologic intervention or vascular BD needing surgical input. Functional rehabilitation, an often-underutilized component of BD management, addresses the musculoskeletal limitations, fatigue, and psychosocial burden associated with chronic inflammation and disability. Physical medicine and rehabilitation physicians can design individualized programs incorporating physiotherapy, occupational therapy, and cognitive-behavioral strategies, while rheumatologists coordinate systemic disease control to optimize functional recovery. This review synthesizes current evidence on the multisystemic challenges of BD, highlighting advances in diagnostic precision, targeted therapy, and rehabilitation. By framing BD management as a coordinated, multidisciplinary approach with rheumatology at its core, we aim to provide clinicians with a comprehensive framework for improving patient-centered outcomes across the disease spectrum.

Keywords: Multidisciplinary Management, Behcet's Disease, Diagnosis

INTRODUCTION

Behcet's disease (BD) is a chronic, relapsing vasculitis of variable vessel size, capable of affecting arteries and veins across multiple organ systems. First described by Hulusi Behçet in 1937 as a triad of recurrent oral ulcers, genital ulcers, and uveitis, the disease is now recognized as a heterogeneous systemic disorder encompassing mucocutaneous, ocular, vascular, neurological, gastrointestinal, and musculoskeletal involvement. Its epidemiological prevalence is most prominent along the historical Silk Road—stretching from the Mediterranean basin through the Middle East to East Asia—yet cases are increasingly identified in non-endemic regions, reflecting migration patterns and growing clinical awareness [1].

The multisystemic nature of BD presents significant diagnostic and therapeutic challenges. Clinical manifestations often arise asynchronously, mimicking other systemic autoimmune and autoinflammatory disorders, thereby delaying diagnosis and timely intervention. Moreover, disease activity is unpredictable, with flares and remissions that may result in cumulative organ damage over time. The morbidity and mortality burden is highest among patients with ocular, vascular, and neurological involvement, where irreversible complications such as blindness, aneurysmal rupture, and disabling parenchymal brain injury can occur [2].

Rheumatologists are uniquely positioned to lead BD management team due to their expertise in systemic inflammatory and vasculitis syndromes. However, effective care requires the integration of multiple specialties: ophthalmology for rapid vision-preserving interventions, neurology for managing neuro-Behcet's disease, vascular surgery for aneurysm repair and thrombotic complications, dermatology for cutaneous control, gastroenterology for intestinal involvement, and physical medicine and rehabilitation for optimizing functional outcomes. In this context, the rheumatologist serves as both diagnostic and care coordinator, ensuring therapeutic decisions are made within a unified, patient-centered framework [3].

Advances in imaging modalities, biomarker discovery, and targeted therapeutics have begun to address long-standing diagnostic and treatment gaps. Likewise, the incorporation of structured rehabilitation strategies offers a pathway to preserve physical function, reduce disability, and improve quality of life. Yet, the integration of these elements into routine BD care remains inconsistent across healthcare systems, underscoring the need for multidisciplinary protocols and shared decision-making models [4].

This review aims to delineate the clinical complexity of BD, emerging diagnostic and therapeutic advances, and highlight the essential role of rehabilitation within a multidisciplinary care paradigm. By framing BD management as a coordinated effort anchored in rheumatology but enriched by other specialties collaboration, we propose a model capable of addressing the full spectrum of patient needs, from acute disease control to long-term functional recovery.

Epidemiological and clinical spectrum of Behçet's disease

Behcet's disease (BD) demonstrates marked geographic variation in prevalence, reflecting both genetic predisposition and environmental influences. The highest prevalence rates were reported in Turkey (up to 420 cases per 100,000 population), followed by Iran, Japan, and other countries along the Silk Road corridor [5]. In Europe and North America, BD remained rare, with prevalence estimates ranging from 0.1 to 7 per 100,000 but rising recognition among immigrant populations has shifted the epidemiological profile [6]. The disease typically presented in young adulthood, with a slight male predominance in high-prevalence regions and more balanced gender distribution in low-prevalence areas. Men tended to have more severe vascular and ocular involvement, whereas women more frequently exhibited mucocutaneous and articular manifestations [7].

Clinically, BD was reported to be characterized by recurrent oral aphthous ulcers, occurring in nearly all patients and often serving as the initial symptom. Genital ulcers, which may heal with scarring, were detected in 60–80% of cases. Cutaneous lesions—such as erythema nodosum-like nodules, papulopustular eruptions, and acneiform lesions—reflected the neutrophil-rich inflammatory environment of BD [8]. Musculoskeletal involvement, most commonly presenting as non-erosive, recurrent mono- or oligoarthritis, affected up to half of patients and could cause functional impairment during flares [9].

Ocular disease, a major cause of morbidity, affected 30–70% of BD patients depending on geographic location. Panuveitis and retinal vasculitis were the most typical lesions, often bilateral and recurrent, with a high risk of vision loss if not promptly treated. Vascular involvement was distinctive, affecting both arterial and venous disease, with deep vein thrombosis, pulmonary artery aneurysms, and large-vessel occlusions among the most serious complications [10].

Neurological manifestations, classified as parenchymal and non-parenchymal neuro-Behçet's disease (NBD), occur in 5–10% of patients. Parenchymal NBD often affected the brainstem and deep gray matter, causing focal deficits and cognitive changes, while non-parenchymal NBD typically presented as cerebral venous sinus thrombosis. Gastrointestinal BD, more prevalent in East Asia, could mimic inflammatory bowel disease, with deep ulcerations most often detected in the ileocecal region [11].

The multisystemic nature of BD necessitates broad clinical attention. Manifestations may appear sequentially over years, complicating early diagnosis. This evolving presentation underscores the need for rheumatologists to maintain long-term surveillance and coordinate with other subspecialists to detect organ-threatening complications before irreversible damage occurs [12].

Diagnostic challenges and advances

Diagnosing Behcet's disease (BD) remains challenging due to its absence of pathognomonic laboratory markers and the heterogeneous, often sequential emergence of clinical features. The diagnosis is primarily clinical, based on the recognition of characteristic symptom clusters and exclusion of mimicking disorders such as systemic lupus erythematosus, inflammatory bowel disease, and other vasculitides. Rheumatologists often encounter patients early, when only one or two manifestations are present, necessitating a high index of suspicion and longitudinal follow-up [13].

The International Criteria for Behçet's Disease (ICBD), updated in 2014, provide a weighted point-based system incorporating oral ulcers, genital ulcers, ocular lesions, skin lesions, neurological manifestations, and vascular involvement. These criteria improve sensitivity compared to the older International Study Group (ISG) criteria, particularly in early disease, but specificity may be reduced in low-prevalence regions. In rheumatology practice, criteria are best applied as a guide for classification rather than a rigid diagnostic tool, with clinical judgment remaining paramount [14].

Advances in imaging have significantly enhanced early and precise detection of organ involvement. High-resolution Doppler ultrasound and MR angiography allowed non-invasive assessment of vascular lesions, including deep vein thrombosis [15]. In ophthalmology collaboration, optical coherence tomography (OCT) and fluorescein angiography have improved the detection and monitoring of retinal vasculitis. Neuroimaging, particularly magnetic resonance imaging (MRI) with contrast, remained the gold standard for evaluating parenchymal neuro-Behçet's disease, with characteristic findings in the brainstem, thalamus, and basal ganglia [16].

Emerging biomarkers offer potential to supplement clinical assessment. Elevated levels of circulating endothelial cells, neutrophil extracellular trap (NET) components, and cytokines such as interleukin (IL)-6 and IL-17 have been associated with disease activity and specific organ involvement [17]. Genetic testing for HLA-B51, while not diagnostic, may support the diagnosis in equivocal cases, especially in endemic areas. Salivary and fecal microbiome analysis was also investigated for diagnostic and prognostic utility [18].

Point-of-care tools integrating clinical criteria, imaging, and biomarker profiles may represent the future of BD diagnosis, particularly in rheumatologists-led multidisciplinary clinics. Such integrative approaches could shorten diagnostic delays, facilitate earlier intervention, and reduce irreversible organ damage [19].

Mucocutaneous disease management

Mucocutaneous lesions were reported to be the most common and earliest manifestations of Behçet's disease (BD), serving as important diagnostic clues for rheumatologists. Oral aphthous ulcers occured in nearly all patients, typically presenting as recurrent, painful, shallow lesions on the buccal mucosa, tongue, or lips, with healing over 1–3 weeks. Genital ulcers, although less frequent, were deeper, more scarring, and associated with higher patient-reported morbidity. Cutaneous manifestations included erythema nodosum–like nodules, papulopustular eruptions, acneiform lesions, and superficial thrombophlebitis, often reflecting neutrophil-driven inflammation [20].

Management goals for mucocutaneous BD are to reduce lesion frequency, accelerate healing, and improve quality of life while minimizing the use of systemic immunosuppression. Topical corticosteroids (e.g., triamcinolone acetonide paste for oral ulcers, potent steroid creams for cutaneous lesions) and local anesthetics were defined to be first line for mild disease. Sucralfate suspension might provide symptomatic relief for oral lesions. For patients with frequent or severe mucocutaneous flares, colchicine remained a cornerstone therapy, particularly effective in erythema nodosum and arthritis, and widely used in rheumatology practice due to its favorable safety profile [21].

When colchicine became insufficient, systemic immunosuppressants such as azathioprine, cyclosporine, and thalidomide were considered. Azathioprine has demonstrated efficacy in reducing oral and genital ulcer recurrence and in preventing progression to major organ involvement, making it a preferred choice in patients with multisystem disease [22]. Thalidomide use, while highly effective for refractory mucocutaneous lesions, was limited by teratogenicity and peripheral neuropathy risk, necessitating careful patient selection and monitoring [23].

Biologic agents were increasingly employed in refractory cases. Anti-tumor necrosis factor (TNF) therapies, such as infliximab and adalimumab, had shown rapid efficacy in severe ulcerative disease unresponsive to conventional immunosuppression, often as part of broader systemic disease control [24]. IL-1 inhibitors, including anakinra and canakinumab, have been reported to reduce mucocutaneous flares in selected patients with prominent innate immune activation [25].

Coordination between rheumatologists and dermatologists ensures comprehensive lesion assessment, differential diagnosis (e.g., herpes simplex virus, fixed drug eruptions), and optimal use of topical versus systemic agents. Patients education on triggers avoidance, oral hygiene, and skin care plays a vital role in reducing recurrence and improving treatment adherence [26].

Ocular disease management

Ocular involvement in Behçet's disease (BD) was reported to be one of the most severe and vision-threatening manifestations, occurring in up to 70% of patients in high-prevalence regions and often within the first few years of disease onset. The most common reported presentations were recurrent, bilateral panuveitis and occlusive retinal vasculitis, which could progress rapidly to irreversible vision loss without prompt intervention [27]. Inflammation might involve the anterior, intermediate, or posterior segments, but posterior uveitis and panuveitis carried the greatest risk for permanent structural damage to the retina and optic nerve [28].

The primary goal of ocular BD management is to suppress intraocular inflammation swiftly and maintain long-term remission to preserve visual function. Given the risk of rapid deterioration, urgent referral to ophthalmology is essential at the first sign of ocular involvement. Rheumatologists were reported to play a key role in initiating systemic immunosuppressive therapy and coordinating care with ophthalmologists experienced in uveitis management [29].

First-line systemic treatment typically involved high-dose corticosteroids (oral or intravenous methylprednisolone) to control acute inflammation, followed by a steroid-sparing immunosuppressant to reduce relapse risk. Azathioprine was widely used and has demonstrated efficacy in preventing ocular flares and preserving vision [30]. Cyclosporine was particularly effective in controlling posterior segment inflammation, although its use requires careful monitoring for nephrotoxicity and hypertension [31].

Biologic therapies have been used in the management of severe ocular BD, especially in patients refractory to conventional agents. Anti-TNF agents such as infliximab and adalimumab provided rapid suppression of uveitis and were often employed as a second-line therapy in sight-threatening disease [32]. Interferon-alpha had also shown benefit in refractory cases, though side effects might limit its use [33]. Recent reports suggested a potential role for IL-6 receptor blockade (tocilizumab) and IL-1 inhibition (anakinra, canakinumab) in resistant ocular inflammation, particularly in patients with concurrent systemic disease activity [34].

Close rheumatologists–ophthalmologists collaboration allowed for timely therapeutic escalation, individualized monitoring of drug toxicity, and coordinated imaging follow-up using fluorescein angiography and optical coherence tomography (OCT). Regular patients education on early symptoms recognition—such as floaters, photophobia, and blurred vision—could prompt rapid medical review and prevent irreversible damage [35].

Vascular disease management

Vascular involvement in Behçet's disease (BD) was reported to be distinctive in that it could affect both arteries and veins of all sizes, with a strong predilection for venous thrombosis and aneurysm formation . Deep vein thrombosis (DVT) of the lower extremities was the most common presentation, followed by superficial thrombophlebitis, vena cava thrombosis, and, less frequently, pulmonary artery aneurysms or large-artery occlusions. Arterial lesions, particularly pulmonary artery aneurysms, were found to be life-threatening due to the risk of rupture [36].

Pathophysiologically, BD-related vascular disease was reportd to be thromboinflammatory. Endothelial injury from neutrophil

hyperactivation, cytokine-mediated inflammation, and oxidative stress could trigger a prothrombotic state, often in the absence of conventional thrombophilia markers. This inflammatory basis supported the principle that immunosuppression—not anticoagulation alone—is the cornerstone of therapy [37].

For acute venous thrombosis, high-dose corticosteroids combined with immunosuppressants such as azathioprine, cyclophosphamide, or cyclosporine were recommended to control vascular inflammation and prevent extension or recurrence [38]. Biologic agents, particularly anti-TNF therapies, were increasingly employed for refractory or relapsing vascular disease, and studies have demonstrated their role in reduction in thrombotic relapses and improved vessel patency [39].

The role of anticoagulation in BD remained controversial. While anticoagulation might be beneficial in preventing thrombus propagation in certain venous lesions, it carried significant bleeding risk in patients with coexisting arterial aneurysms, especially pulmonary artery aneurysms. Many guidelines recommended anticoagulation only after aneurysmal disease was excluded through appropriate imaging and under close multidisciplinary supervision [40].

Surgical or endovascular intervention was reported to be necessary, particularly for large or ruptured aneurysms, severe occlusive disease, or complications such as vena cava syndrome. Preoperative and postoperative immunosuppression was essential to minimize postoperative inflammatory flares and restenosis risks. Collaboration between rheumatologists, vascular surgeons, and interventional radiologists ensured optimal timing, procedural selection, and postoperative monitoring [41].

Long-term follow-up with vascular imaging, aggressive inflammation control, and patient education on early signs of vascular complications were essential to reducing morbidity and mortality. Rheumatologists remain central to coordinating this care, balancing immunosuppressive therapy with vascular-specific interventions to optimize outcomes [42].

Neurological involvemnt management

Neurological involvement in Behçet's disease (BD), termed neuro-Behçet's disease (NBD), was reported in approximately 5–10% of patients and was among the most disabling manifestations. NBD is broadly categorized into parenchymal and non-parenchymal forms. Parenchymal NBD was suggested to be driven by inflammatory vasculitis affecting the brainstem, basal ganglia, and diencephalon, leading to subacute onset of focal neurological deficits, pyramidal signs, cranial neuropathies, and, in some cases, cognitive or psychiatric changes [43]. Non-parenchymal NBD was suggested to result from cerebral venous sinus thrombosis (CVST) secondary to large-veins inflammation, presenting with headache, papilledema, and increased intracranial pressure [44].

Early diagnosis is crucial, as irreversible neuronal injury can occur with delay in treatment. MRI with gadolinium contrast is the imaging modality of choice for parenchymal disease, revealing T2 hyperintense lesions in the brainstem and deep white matter, while MR venography is essential for diagnosing CVST. Cerebrospinal fluid (CSF) analysis often shows mild pleocytosis and elevated protein in parenchymal NBD but may be normal in non-parenchymal disease [45].

Management of NBD was reported to be by aggressive immunosuppression tailored to the subtype. For parenchymal NBD, high-dose intravenous methylprednisolone followed by oral steroids with a slow tapering was standard initial therapy. Immunosuppressants such as azathioprine, cyclophosphamide, or mycophenolate mofetil were commonly added for relapse prevention [46]. Anti-TNF agents, particularly infliximab, have shown efficacy in refractory parenchymal disease, with some evidence suggesting that earlier use may improve long-term neurological outcomes [47].

Non-parenchymal NBD management was reported to focus on controlling vascular inflammation with corticosteroids and immunosuppressants. The role of anticoagulation in CVST remained debated, but it might be considered in selected cases after aneurysmal disease was excluded and under multidisciplinary supervision. Close rheumatologists–neurologist coordination was reported to be essential to balance immunosuppression, anticoagulation, and neurological monitoring [48].

Long-term follow-up was reported to be vital, as both parenchymal and non-parenchymal NBD carried a risk of relapse and cumulative disability. Rehabilitation services, including physiotherapy, speech therapy, and cognitive rehabilitation, should be integrated early to optimize recovery. Rheumatologists, as central coordinators, ensure that disease control is maintained while neurological function is maximized through a multidisciplinary approach [49].

Gastrointestinal and other organs involvement

Gastrointestinal Behçet's disease (BD) was reported to be most prevalent in East Asian populations, particularly in Japan and

Korea, where it might affect up to 25% of patients. The disease predominantly was found to involve the ileocecal region, producing deep, punched-out ulcerations that can mimic Crohn's disease both clinically and endoscopically. Symptoms included abdominal pain, diarrhea, and gastrointestinal bleeding, with severe cases progressing to perforation or massive hemorrhage [50]. Differentiating intestinal BD from inflammatory bowel disease was reported to be critical, as treatment strategies and prognosis differed. Histopathology often revealed nonspecific vasculitis changes, and absence of granulomas which may aid in distinction [51]

Management of intestinal BD was reported to require a combination of systemic immunosuppression and gastrointestinal interventions. Corticosteroids were used for acute flares, while azathioprine, 6-mercaptopurine, or methotrexate might maintain remission. Biologic agents such as infliximab and adalimumab have demonstrated significant efficacy in refractory cases, improving both endoscopic and clinical outcomes [52]. Thalidomide has also been used with success in East Asian cohorts, though adverse effects limited its use. Close collaboration between rheumatologists and gastroenterologists ensured appropriate monitoring, dietary counseling, and surveillance for complications [53].

Pulmonary involvement in BD was found to be less common but often life-threatening, most notably in the form of pulmonary artery aneurysms. These lesions could cause massive hemoptysis and require urgent immunosuppressive therapy typically high-dose corticosteroids with cyclophosphamide or infliximab [54]. Interventional radiology or surgical repair might be needed for rupture, but always in conjunction with intensive immunosuppressive cover [55].

Other organ systems was found to be involved sporadically. Renal disease, usually secondary to amyloidosis or glomerulonephritis, was rare but carried significant morbidity. Cardiac manifestations, including endomyocardial fibrosis, pericarditis, and intracardiac thrombi, have been described. Genitourinary lesions beyond genital ulcers were uncommon but might occur in severe systemic disease [56].

Given the diverse systemic reach of BD, rheumatologist must maintain vigilance for less common organ involvement, employing a low threshold for multidisciplinary referral. Tailoring therapy to address both systemic inflammation and organ-specific pathology was reported to be essential in improving long-term survival and quality of life [57].

Multidisciplinary care models

The multisystemic nature of Behçet's disease (BD) necessitates an integrated care framework in which rheumatologists function as the central hub, coordinating interventions across multiple specialties. This model is particularly critical in BD, where disease activity can shift rapidly from one organ system to another, and where simultaneous involvement of ocular, vascular, neurological, and gastrointestinal systems is not uncommon [58]. A coordinated approach not only expedites diagnosis and treatment but also minimizes breaking of care and reduces the risk of irreversible organ damage.

Rheumatologists lead BD management by establishing diagnosis, monitoring systemic inflammation, and guiding immunosuppressive strategies. Ophthalmologists provide rapid evaluation and intervention for uveitis and retinal vasculitis, often in close coordination with systemic therapy initiation. Neurologists manage neuro-Behçet's disease, particularly parenchymal involvement, with MRI monitoring and input on neurological rehabilitation. Vascular surgeons and interventional radiologists address and manage aneurysms, large vessel thromboses, and complex occlusions, ideally after immunosuppressive control has been achieved to reduce perioperative complications [59].

Dermatologists contribute to the management of mucocutaneous lesions, guiding topical therapies, differential diagnosis of skin manifestations. Gastroenterologists play a pivotal role in intestinal BD management, coordinating endoscopic surveillance and nutritional management. Physical medicine and rehabilitation specialists are integral in addressing functional decline, particularly in patients with musculoskeletal, neurological, or vascular sequelae, designing individualized rehabilitation programs to preserve mobility and independence [60].

Effective multidisciplinary BD care models often employ regular case follow-ups, shared electronic health records, and standardized treatment pathways that allow rapid escalation when new organ involvement emerges. Specialized nurse coordinators can improve patients' adherence to treatment and communication, ensuring timely follow-up and education on disease monitoring [61].

Longitudinal, multidisciplinary care has been shown to reduce hospitalization rates, prevent vision loss in ocular BD, and improve survival in vascular BD. By integrating each specialist's expertise into a cohesive treatment plan, rheumatology-led multidisciplinary teams can deliver precision care that addresses both acute disease control and long-term functional outcomes [62].

Functional rehabilitation strategies

Functional rehabilitation in Behçet's disease (BD) is often underemphasized despite its critical role in preserving mobility, reducing disability, and improving quality of life. Chronic inflammation, recurrent joint flares, neurological deficits, and vascular complications can result in lasting physical limitations. Rheumatologists, while focused on systemic inflammation control, must work closely with physical medicine and rehabilitation specialists to address the functional consequences of disease [63].

Musculoskeletal manifestations—particularly recurrent, non-erosive arthritis—can lead to muscle weakness, reduced joint range of motion, and deconditioning. Early referral to physiotherapy during or after flares allows for gentle mobilization, prevention of contractures, and maintenance of muscle strength. Structured exercise programs, incorporating low-impact aerobic activities, stretching, and resistance training, have been shown to improve fatigue and functional endurance without exacerbating inflammation [64].

In neuro-Behçet's disease, functional deficits may include hemiparesis, ataxia, dysarthria, and cognitive changes. Rehabilitation strategies in these cases extend beyond physical therapy to include speech therapy, occupational therapy, and neuropsychological support. Task-specific training, balance exercises, and compensatory techniques help restore independence in daily activities. Assistive devices, from walking aids to adaptive home modifications, should be considered early to optimize safety and prevent falls [65].

Vascular complications such as deep vein thrombosis or large-vessel occlusions may necessitate tailored rehabilitation approaches that care for limb swelling, pain, or reduced perfusion. Graduated compression therapy, supervised ambulation programs, and progressive strengthening exercises can be implemented once acute inflammation is controlled and vascular stability is confirmed [66].

Psychosocial rehabilitation is equally important. Chronic pain, disfigurement from mucocutaneous lesions, vision loss, and neurological disability can contribute to depression and social withdrawal. Integrating cognitive-behavioral therapy, patient support groups, and vocational rehabilitation into the management plan enhances mental well-being and facilitates return to work or education. Rheumatologists should ensure that these supportive services are offered alongside pharmacologic management [67].

Ultimately, rehabilitation in BD is most effective when embedded in a multidisciplinary framework, with rheumatology guiding systemic control and rehabilitation medicine addressing functional recovery. Regular reassessment ensures that rehabilitation goals adapt to changes in disease activity and patient priorities, supporting long-term independence and quality of life [68].

Emerging precision medicine approaches in Behçet's disease

Precision medicine in Behçet's disease (BD) has evolved in response to the wide heterogeneity of disease presentation, where clinical manifestations range from isolated mucocutaneous lesions to rapidly progressive ocular, vascular, or neurological involvement. Rather than applying a uniform treatment algorithm, therapy is increasingly tailored to the specific organ systems involved, severity of presentation, recurrence risk, and underlying immunoinflammatory drivers. Rheumatologists, as the central coordinators of BD care, integrate these variables with patient comorbidities and preferences, while collaborating with subspecialists to optimize both systemic disease control and long-term function [69].

Mucocutaneous involvement—comprising oral aphthous ulcers, genital ulcers, and neutrophilic skin lesions such as erythema nodosum–like nodules or papulopustular eruptions—remains the most common manifestation and is often the first to appear. Colchicine is the first-line systemic treatment, particularly effective for erythema nodosum and arthritis-associated skin lesions. Topical corticosteroids and sucralfate mouth rinse are routinely used for symptomatic relief. In patients with frequent or severe ulcerations unresponsive to colchicine, systemic immunosuppressants such as azathioprine or thalidomide may be considered, the latter requirs strict monitoring for teratogenicity and neuropathy. For refractory mucocutaneous disease, biologics such as adalimumab or infliximab are effective, while IL-1 inhibitors (anakinra, canakinumab) may be particularly useful in phenotypes driven by innate immune hyperactivation [70].

Ocular BD, characterized by recurrent uveitis and retinal vasculitis, requires urgent and aggressive therapy to prevent irreversible vision loss. High-dose systemic corticosteroids, given orally or intravenously, are the mainstay of acute inflammation control, but are rapidly combined with steroid-sparing immunosuppressants to minimize long-term toxicity. Azathioprine remains a preferred first-line maintenance agent, while cyclosporine is highly effective in posterior segment disease but contraindicated in neuro-Behçet's due to CNS toxicity risk. Infliximab and adalimumab are favored biologics for sight-threatening or refractory ocular BD, with interferon-alpha offering an alternative in select cases. Tocilizumab and IL-1 blockade have shown promise in small series for biologic-refractory ocular inflammation [71].

Vascular involvement in BD is distinct among vasculitides, with a predilection for both venous thrombosis and arterial aneurysm formation. The core therapeutic principle is that inflammation must be controlled first. Acute venous thromboses are treated with high-dose corticosteroids combined with immunosuppressants such as azathioprine or cyclophosphamide, with anti-TNF agents increasingly used for refractory or recurrent vascular disease. Pulmonary artery aneurysms require urgent high-dose immunosuppression, often cyclophosphamide, with surgical or endovascular repair deferred until inflammation is controlled to reduce perioperative complications. Anticoagulation is reserved for selected venous cases after careful exclusion of aneurysms by vascular imaging [72].

Neurological involvement, or neuro-Behçet's disease (NBD), is classified into parenchymal and non-parenchymal forms, each with distinct management strategies. Parenchymal NBD—most often affecting the brainstem and deep white matter—requires high-dose intravenous methylprednisolone followed by a slow taper, alongside azathioprine or cyclophosphamide for relapse prevention. Anti-TNF agents such as infliximab are increasingly used for refractory or aggressive parenchymal disease. Non-parenchymal NBD, typically presenting as cerebral venous sinus thrombosis, is managed with immunosuppression; anticoagulation remains controversial and is individualized based on aneurysm status and multidisciplinary input [73].

Gastrointestinal BD, most prevalent in East Asia, commonly involves deep ulcerations in the ileocecal region, producing abdominal pain, diarrhea, and bleeding. Acute flares are treated with corticosteroids, followed by maintenance therapy with azathioprine, 6-mercaptopurine, or methotrexate. Infliximab and adalimumab are highly effective for refractory intestinal disease, improving both clinical and endoscopic outcomes, while thalidomide remains an option in selected refractory cases under strict monitoring. Differentiating intestinal BD from Crohn's disease is essential, as therapeutic strategies and biologic selection differ [74].

Musculoskeletal manifestations in BD, usually non-erosive, recurrent mono- or oligoarthritis, respond well to colchicine and NSAIDs. Persistent synovitis may warrant azathioprine or methotrexate, while anti-TNF therapy is effective for severe or refractory cases, particularly when arthritis occurs alongside other systemic disease activity. Early physiotherapy is recommended to preserve range of motion and prevent deconditioning, especially after acute flares [75].

Rehabilitation and supportive care are integral to precision medicine in BD, addressing functional impairments resulting from vascular, neurological, or ocular damage. Physiotherapy, occupational therapy, and vision rehabilitation programs are tailored to patient needs and adjusted dynamically according to disease activity. Psychosocial interventions, including counseling and cognitive-behavioral therapy, help mitigate the psychological burden of chronic pain, disfigurement, and disability. Embedding rehabilitation into the multidisciplinary care model ensures that functional recovery is pursued in parallel with systemic inflammation control [76].

Conclusion and future directions

Behçet's disease (BD) represents one of the most challenging systemic vasculitides to manage due to its unpredictable course, multisystem involvement, and variable clinical severity. Over the past two decades, advances in understanding the genetic, immunologic, and vascular bases of BD have significantly expanded the therapeutic management, enabling rheumatologists to move from empiric, symptom-driven regimens toward targeted, phenotype-specific interventions. The increasing integration of biologics, small-molecule inhibitors, and genotype-informed strategies signals the early maturation of precision medicine in BD.

The multidisciplinary model—anchored by rheumatology and enriched by ophthalmology, neurology, vascular surgery, dermatology, gastroenterology, and physical medicine—has emerged as the optimal framework for proper care delivery. This collaborative approach not only addresses acute, organ-threatening complications but also supports long-term functional recovery through rehabilitation, psychosocial support, and patient education. Embedding standardized referral pathways, joint specialty clinics, and shared decision-making tools into practice can improve outcomes while reducing care breakdown.

Future priorities include the development of validated biomarkers to guide early diagnosis, predict flares, and inform therapeutic selection. Large, multicenter randomized controlled trials are urgently needed to define the comparative efficacy of emerging biologics and small molecules in specific BD phenotypes, such as vascular-predominant or neuro-Behçet's disease. Translational research linking immunologic signatures, genetic profiles, and microbiome composition to clinical outcomes will be essential for patient stratification and optimizing treatment sequencing.

Rehabilitation research remains a neglected aspect in BD management. Systematic evaluation of physiotherapy protocols, occupational adaptations, and neurocognitive interventions could better define their role in maintaining independence and quality of life. Similarly, digital health tools, including mobile disease activity tracking, telemedicine follow-up, and patient-reported outcome measures, are promising approaches for improving access to multidisciplinary care, particularly in geographically remote settings.

Ultimately, the future of BD management lies in merging mechanistic insight with coordinated clinical delivery. Precision medicine and multidisciplinary care are not parallel strategies but intersecting pillars of a comprehensive approach—capable of controlling inflammation, preventing irreversible damage, and empowering patients to enjoy a good life despite the challenges of this complex disease. For rheumatologists, embracing this integrated vision is both an opportunity and a responsibility in the evolving landscape of BD care.

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