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BSR Guidelines

Guidelines

British Association of Dermatologists and British Society for Rheumatology living guideline for managing people with Behçets 2024

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NICE has renewed accreditation of the process used by the British Association of Dermatologists to produce clinical guidelines. The renewed accreditation is valid until 31 May 2026 and applies to guidance produced using the processes described in the updated guidance for writing a British Association of Dermatologists clinical guideline – the adoption of the GRADE methodology 2016. The original accreditation term began on 12 May 2010. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

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This is a living guideline prepared for the British Association of Dermatologists (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines Subcommittee; and for the British Society for Rheumatology (BSR), including the Guidelines Steering Group. Members of the BAD's Clinical Standards Unit who have been involved are S.L. Chua (Chair,

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1.0 Purpose and scope

The overall objective of the current iteration of this living guideline is to provide up-to-date, evidence-based recommendations for the management of Behçets disease/syndrome (henceforth termed 'Behçets' for simplicity, and as approved by the patient support group) in adults, children and young people. The document aims to:

- offer an appraisal of all relevant literature up to 25 August 2023 focusing on any key developments
- address important, practical clinical questions relating to the primary guideline objective
- provide guideline recommendations and appropriate research recommendations.

The guideline is presented as a detailed review with highlighted recommendations for practical use in all appropriate community and hospital settings (see Section 3.0), in addition to a patient information leaflet (PIL; available on the BAD website: www.skinhealthinfo.org.uk).

2.0 Methodology

This guideline has been developed using the BAD's recommended methodology.[1] Further information can be found in Appendix L (see Supporting Information) with reference to the AGREE II instrument (www.agreetrust.org)[2] and GRADE[3] (Appendix L). While the recommendations were developed for anticipated implementation in the UK National Health Service (NHS), they could equally be adapted in other healthcare systems, internationally, acknowledging different countries' health systems, including their priorities, legislation, drug availabilities, funding and policies.

The Guideline Development Group (GDG) consisted of four consultant dermatologists (RM, IC, JS, CW), five consultant rheumatologists (RJM, ASMJ, PB, CEP, PS), among whom two were paediatric consultant rheumatologists (PB, CEP), one consultant gastroenterologist (AFC), one consultant ophthalmologist (HP), two consultants in oral medicine (JS, APG), one consultant neurologist (SK), one consultant in obstetrics and gynaecology (MCJ), three clinical psychologists (SC, JH, SH), one dermatology registrar (SSK), one rheumatology registrar (APC), one pharmacist (HM), two people with lived experience of Behçets (LF, RW) and a technical team, which consisted of one information scientist (MH), two guideline research fellows (LM, AMC) and a project manager (MFMM) providing methodological and technical support.

The GDG established one systematic review question pertinent to the scope of the guideline and a set of outcome measures of importance to people with Behçets, ranked according to the GRADE methodology[4] (see Section 2.1; and Appendix A in the Supporting Information).

A systematic literature search of the PubMed, MEDLINE, Embase and Cochrane databases was conducted by the technical team to identify key articles on Behçets up to 25 August 2023. The search terms and strategies are detailed in Appendix M (see Supporting Information). Additional references relevant to the topic were also isolated from citations in the reviewed literature. Data extraction and critical appraisal, data synthesis, evidence summaries, lists of excluded studies and the PRISMA flow diagram were prepared by the technical team. The overall certainty of evidence from the studies included in the quantitative review was graded according to the GRADE system (high, moderate, low or very low certainty).

In making these recommendations, all GDG members have evaluated the entire dataset obtained from the living systematic review of the literature pertaining to the clinical question of interest (Section 2.1).

The recommendations were made in discussion with the entire GDG, including people with lived experience of Behçets, considering all factors that would affect the strength of the evidence, according to the GRADE approach (i.e. balance between desirable and undesirable effects, quality of evidence, patient values and preferences, and resource allocation). All GDG members contributed towards drafting and/or reviewing the narratives and appendices in the Supporting Information. When insufficient evidence from the literature was available, informal consensus was reached based on the expert opinion of the GDG.

The Supporting Information includes summaries of the findings with forest plots (Appendix B), tables Linking the Evidence To the Recommendations (LETR) (Appendix C), GRADE evidence profiles indicating the certainty of evidence (Appendix D), summaries of the included systematic reviews (Appendix E), summaries of the comparative studies included in the quantitative and qualitative syntheses (Appendix F), narrative findings from noncomparative studies (Appendix G), PRISMA flow diagram (Appendix H), critical appraisals of the included systematic reviews using AMSTAR-2 (Appendix I), risk-of-bias analyses (Appendix J) and lists of excluded studies (Appendix K).

The strength of recommendation is expressed by the wording and symbols shown in Table 1.

Applicability of the recommendations to clinical practice is outlined in Sections 3.2, 4.0, 5.7, 5.8 and 5.10. A 'patient values and preferences' section and further discussion of the included evidence, treatment options, practical and economic considerations and service provision is also featured in the LETR narrative (Appendix C).

2.1 Clinical questions and outcomes

The GDG established a systematic review question pertinent to the scope of the guideline. See Appendix A for the full living systematic review protocol.

The GDG also established a set of outcome measures of importance to people with Behçets, which were agreed by people with lived experience of Behçets and ranked according to the GRADE methodology.[4] Outcomes ranked 7, 8 or 9 are critical for decision making and those ranked 6 are important, but not critical for decision making.

Table 1. Strength of recommendation

Strength	Wording	Symbol	Definition
Strong recommendation *for* the use of an intervention	'Offer' (or similar, e.g. 'use', 'provide', 'take', 'investigate' etc.)	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention while only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policymakers, it would be a useful performance indicator
Weak recommendation *for* the use of an intervention	'Consider'	↑	Risks and benefits of the intervention are finely balanced; most patients would choose the intervention, but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policymakers it would be a poor performance indicator where variability in practice is expected
No recommendation		Θ	Insufficient evidence to support any recommendation
Strong recommendation *against* the use of an intervention	'Do not offer'	↓↓	Risks of the intervention outweigh the benefits; most patients would *not* choose the intervention while only a small proportion would; for clinicians, most of their patients would *not* receive the intervention

Systematic review question: In people with Behçets, what is the clinical effectiveness and safety of interventions compared with each other or placebo?

Outcomes:

Critical

- Time to disease flares/frequency of flares[a] (9)
- Quality of life, for example Behcet's Disease Quality of Life (BD-QoL), Short Form Health Survey (SF-36), Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI), Chronic Oral Mucosal Disease Questionnaire (COMDQ) (9)
- Pain (9)
- Improvement in disease activity (9)
- Disease activity scores (e.g. Behçet's Disease Current Activity Scale score) (9)
- Induced remission[a] (8)
- Serious adverse effects (grades 3–4), including treatment failure (e.g. secondary) (8)
- Improvement in psychological functioning, for example mood, Patient Health Questionnaire-9 (PHQ-9), Hospital Anxiety and Depression Scale (HADS) (8)
- Laboratory changes in white cell count (WCC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (7)

Important

- Mild adverse effects (grades 1–2) (6)

[a]Overall and/or organ-specific assessment:

- skin and mucocutaneous (e.g. number of episodes of erythema nodosum, number of lesions/ulcers)
- vascular (e.g. occurrence of deep-vein thrombosis)
- ocular (e.g. visual acuity, number of uveitis attacks, ocular lesions)
- gastrointestinal (e.g. ileocecal ulcer)
- nervous system (e.g. central nervous system lesions).

3.0 Summary of recommendations

The following recommendations and ratings were agreed upon unanimously by all members of the GDG, including people with lived experience of Behçets. For further information on the wording used for recommendations and strength of recommendation ratings see Section 2.0. The GDG is aware of the lack of high-certainty evidence for some of these recommendations; therefore strong recommendations with an asterisk (*) are based on available evidence, as well as consensus within the GDG and specialist experience. Good practice point (GPP) recommendations are derived from informal expert consensus.

3.1 General considerations

The GDG set out to provide an up-to-date, holistic and evidence-based approach to optimize the management of people with Behçets, factoring in patient values and preferences.

Behçets can present in different ways, depending on which organs are involved. This means that multispecialty input is needed to optimize disease management. With the advent of targeted therapies, there are currently 62 clinical trials registered on clinicaltrials.gov[5] for the treatment of this condition (Appendix O; see Supporting Information).

Although several classes of drugs can be used to treat various Behçets-associated symptoms, the majority of these medications are not licensed for this condition. Furthermore, some recommended interventions may not be widely available in the UK.

3.2 Recommendations

All recommendations that employ the term *people* refer to adults, children and young people. The terms 'female', 'male', 'women' and 'men' used throughout this living guideline refer to the sex assigned at birth.

Approaches to therapy

While Behçets is a rare disorder, in the UK the mucocutaneous variant is the most common presentation. In recent years, the development of targeted monoclonal therapies has led to therapeutic advances in disease management. Affected individuals usually report recurrent aphthous-type ulcers of varying severity, in the oral cavity and anogenital region, in conjunction with a range of often nonspecific inflammatory skin lesions such as erythema nodosum, pyoderma gangrenosum and acneiform lesions. These individuals may also describe lethargy and arthralgia (see **R14–R31**).

When considering therapeutic escalation, always take into account the overall disease control and any relevant associated disease affecting other organs that might require systemic therapy to prevent organ damage or reduce disease flares and improve quality of life (QoL). Given the extent of

organs that may be affected in Behçets, multiple medical specialties are needed to optimize patient care. Where possible, this should include awareness of the psychological impact of a rare disorder that is difficult to diagnose and can be challenging to manage effectively (see **R1–R13** and **R84–R87**).

Corticosteroids (CS) are of benefit in Behçets to provide disease control during flares or to test whether the affected individual is likely to benefit from longer-term immunosuppression. CS may be given orally or parenterally according to disease severity and patient factors. CS may be used as initial adjunctive therapy with the initiation of an immunosuppressant (e.g. azathioprine) until therapeutic efficiency is reached. Given the extensive adverse-effect profile of long-term CS, it is advisable to use the lowest dose of CS required, for the shortest time. A frequent or prolonged requirement for CS indicates the need to consider drugs with other mechanisms of action, such as small-molecule immunosuppressants or biologic therapies (see **R14–R17**, **R24–26**, **R32**, **R33**, **R40**, **R43**, **R44**, **R60–R62**, **R64**, **R67**, **R68**, **R71**, **R73–R75**, **R78**).

The treatment strategy for gastrointestinal (GI) Behçets should be based on the reduction of GI symptoms by healing the ulcers, both macroscopically and microscopically, to reduce their associated complications.

Surgery for GI involvement may be needed in treatment-resistant disease when there is a risk of bleeding and or perforation; a temporary stoma may be required to control complications. To avoid repeated anastomotic recurrences and/or complications some patients may need long-term or lifelong, permanent stoma formation (see **R32–R42**).

Manifestation of ocular disease is often the driving factor that leads patients to seek medical attention. Ocular disease in Behçets is sight threatening and, if left untreated, results in complete loss of vision within 4 years in up to 90% of patients. Systemic or intravitreal CS are effective in managing sight-threatening disease. Longer-term therapy with disease-modifying antirheumatic drugs *and* biologics would normally be considered for this group of patients (see **R43–R49**).

A disease flare in Behçets is personalized to the affected individual, with a recognizable set of symptoms. The serological markers for inflammation are often not raised. However, severe flares can lead to endothelial vascular involvement, which increases the risk of arterial aneurysm and venous thrombosis, often present together. Therefore, it is important to manage these acute flares by inducing remission with fast-acting therapies such as high-dose parenteral CS and/or infliximab. In those with established thromboembolic disease, anticoagulation is only recommended in addition to immunosuppressive therapy after arterial involvement and aneurysm formation have been excluded by appropriate imaging, as anticoagulation use in this group is otherwise contraindicated (see **R50–R70** and **R71–R78**).

Behçets is a condition that is often diagnosed and treated in women and those of childbearing age. Ideally, potentially childbearing patients with the condition should be managed in a multidisciplinary setting, including physicians with an interest or expertise in rheumatological conditions and obstetricians with an interest, training or expertise in perinatal medicine. When considering hormonal contraception, it should be noted that some people with Behçets have a potential increased risk of thrombosis.

Women of childbearing age with Behçets should be advised to seek pre-conception counselling from the multidisciplinary team. They can be advised to start taking folic acid and that their condition is unlikely to affect the baby. Most people have an improvement of their symptoms during pregnancy, while only 15–30% will experience a flare,[6] notably oral or genital ulceration. Such ulceration can be treated symptomatically and, usually, topical therapies will suffice. Oral or parenteral CS are also safe.

Before conception, women with Behçets can have their medication reviewed. The majority of medications that are commonly used to treat Behçets are safe in pregnancy; however, it is important that those few women treated with either thalidomide or mycophenolate mofetil[7] must cease treatment prior to actively trying to conceive and should continue with adequate contraception during this time.

The cutaneous condition, pathergy, is more common in individuals with Behçets. This condition is an exaggerated response to skin injury. Following vaginal delivery, vulval and perineal trauma (although often minor) is common. Some women concerned about pathergy may opt for elective caesarean section. These patients should be aware that pathergy can also develop within a caesarean-section wound. This can usually be managed by use of CS, topically or systemically.

Postdelivery, women should be assured that the medications that they have taken during pregnancy are generally safe during breastfeeding too (see **R79–R83**).

Behçets is very rare in children and young people up to the age of 16 years. A UK study showed the 2-year-period prevalence estimate to be 4.2 per million [95% confidence interval (CI) 3.2–5.4], and the incidence was 0.96 per million person-years (95% CI 0.66–1.41). Mucocutaneous disease was the most common variant. Other organ involvement was less common than in adults (ocular 17.9%, neurological 3.6% and vascular 5.4%). Over 83% of children and young people had three or more specialists involved in their care.[8]

General management

R1 (GPP) If Behçets is suspected, convene a multidisciplinary team (MDT) involving core specialties and any other relevant specialties (i.e. dermatology, oral medicine, ophthalmology, gastroenterology, rheumatology and clinical psychology, with neurology and vascular surgery input, where appropriate) when managing people with Behçets of all ages. Children and young people with Behçets should be managed within an MDT appropriate to their age and development. Referral of patients to a national Behçets centre may be indicated to optimize diagnosis and treatment.

R2 (GPP) Consider the criteria of the 1990 International Study Group (ISG) or the International Criteria for Behcet's Disease (ICBD) when diagnosing people with suspected Behçets.

R3 (GPP) Ensure that the assessment of overall disease activity considers both, the Physician's Global Assessment and patient-reported outcomes, or a Behçets-specific disease activity tool.

R4 (GPP) Assess, within the multidisciplinary team, at each visit, the extent of organ involvement and target therapy accordingly, to avoid permanent organ damage.

R5 (GPP) Provide people with Behçets, at the time of diagnosis, with a patient information leaflet (e.g. from the British Association of Dermatologists: www.skinhealthinfo.org.uk/a-z-conditions-treatments) and engage people with Behçets, throughout their treatment pathway, in conversation about their condition to ensure shared decision making.

R6 (GPP) Assess the disease impact, at diagnosis and at each follow-up visit, by employing a quality-of-life assessment tool.

R7 (GPP) Consider an antimetabolite (e.g. methotrexate or azathioprine) with anti-tumour necrosis factor therapy in people with Behçets to prevent or delay production of anti-drug antibodies.

R8 (↓↓) Do not offer* thalidomide to people with Behçets, unless there are exceptional circumstances, due to its adverse effects profile (e.g. teratogenicity and neurotoxicity).

R9 (GPP) Advise people with Behçets who present with severe oral aphthous-like ulcers on simple oral hygiene measures, having regular dental appointments and the use of topical antiseptics (e.g. chlorhexidine mouthwash) and the avoidance of irritants such as sodium lauryl sulfate in toothpaste or any identified food.

R10 (GPP) Be aware that a pathergic response may be triggered in some people following vaccination and/or surgery.

R11 (GPP) Be aware that paradoxical Behçets has been reported in association with interleukin-17 inhibitors.

R12 (GPP) The transition from children's to adults' services should be in line with National Institute for Health and Care Excellence guideline NG43.[9] Transition should be developmentally appropriate and follow a person-centred approach. Point of transfer to adult care should take place at a time of relative stability for the young person and not be based on a rigid age threshold.

R13 (GPP) Prepare a care plan and forward to the patient's general practitioner within 2 weeks of their clinic appointment, noting any specialist advice required (e.g. for changes in medication).

Mucocutaneous

R14 (↑↑) Offer* potent or superpotent topical corticosteroids to treat oral and genital ulcers in people with Behçets if the symptoms are mild, or as adjunctive therapy with systemic immunosuppression for more severe disease. Consider the appropriate formulation of the topical corticosteroids for oral and genital use depending on patient preference and age, as well as ulcer location.

R15 (GPP) Consider the triple mouthwash[§] for oral ulceration in people with Behçets.

[§]The triple mouthwash: betamethasone 500 micrograms soluble tablets + doxycycline 100 mg + 1 mL nystatin oral suspension.

R16 (GPP) Consider potent and superpotent corticosteroids, as a single preparation or in combination with nystatin and neomycin, as treatment for anogenital ulceration in people with Behçets above 12 years of age.

R17 (↑↑) Offer* colchicine as a second-line option to treat mucocutaneous lesions in people with Behçets, where topical corticosteroid therapy alone provides inadequate disease control. Titrate colchicine dosing gradually to minimize any gastrointestinal side-effects.

R18 (↑↑) Offer* azathioprine or mycophenolate mofetil as a third-line monotherapy option or as adjunctive therapy for mucocutaneous lesions in people with Behçets who have poorly controlled symptoms.

R19 (↑↑) Offer anti-tumour necrosis factor therapy as a third- line option to treat mucocutaneous lesions in people with Behçets who have poorly controlled symptoms and/or with other organ involvement refractory to conventional systemic therapies.

R20 (↑) Consider apremilast, where available, as a fourth-line option to treat mucocutaneous lesions in adults with Behçets in whom conventional systemic therapies have failed.

R21 (↑) Consider secukinumab as a fourth-line option to treat mucocutaneous lesions in the absence of gastrointestinal and/or ocular involvement in adults and children aged ≥ 6 years with Behçets who have poorly controlled symptoms and/or with other organ involvement refractory to conventional systemic therapies and in whom anti-tumour necrosis factor therapy has failed or is contraindicated.

R22 (↑) Consider dapsone as a treatment option in people with Behçets.

- **Θ** There is insufficient evidence to recommend topical calcineurin inhibitors for people with Behçets.
- **Θ** There is insufficient evidence to recommend colchicine to treat folliculitis in adults with Behçets.
- **Θ** There is insufficient evidence to recommend sucralfate to treat genital ulcers in people with Behçets.

Arthritis/arthralgia

R23 (↑↑) Offer colchicine as a first-line option to treat arthritis/arthralgia in people with Behçets if there is no other serious organ involvement. To avoid gastrointestinal side-effects, increase the colchicine dose gradually, in line with the manufacturers' recommendations.

R24 (↑↑) Offer an intramuscular depot or a short course of low-dose oral corticosteroids as a second-line option to treat arthritis/arthralgia in adults with Behçets without any serious organ involvement when there is inadequate response to colchicine.

R25 (GPP) Consider nonsteroidal anti-inflammatory drugs (NSAIDs) as an alternative to oral corticosteroids when treating arthritis/arthralgia in people with Behçets without any serious organ involvement if there is no contraindication.

R26 (GPP) Offer intra-articular corticosteroid injection as an option to treat monoarticular or oligoarticular synovitis in people with Behçets.

R27 (↑↑) Offer azathioprine or anti-tumour necrosis factor therapy as options to treat persistent and refractory arthritis/arthralgia in people with Behçets.

R28 (↑) Consider apremilast as an option to treat arthritis/arthralgia in adults with Behçets.

R29 (↑) Consider methotrexate, mycophenolate mofetil or azathioprine as options to treat arthritis/arthralgia in people with Behçets. Caution should be exercised in those with extensive mouth ulceration due to its potential to worsen with methotrexate therapy.

R30 (↑) Consider secukinumab as an option to treat arthritis/arthralgia in adults and children aged ≥ 6 years with Behçets.

R31 (GPP) Consider referral to physiotherapy, occupational therapy and/or podiatry, if symptoms require.

Gastrointestinal

R32 (↑↑) Offer* oral/intravenous corticosteroids as a first-line option to treat acute flares in people with gastrointestinal Behçets.

R33 (↑↑) Taper* systemic corticosteroids on commencing 5-aminosalicylic acid, azathioprine or 6-mercaptopurine in people with gastrointestinal Behçets.

R34 (↑↑) Offer* 5-aminosalicylic acid as a first-line option to treat flares of mild-to-moderate clinical activity in people with gastrointestinal Behçets.

R35 (↑↑) Offer* azathioprine or 6-mercaptopurine as a first- or second-line option to people with gastrointestinal Behçets who have moderate-to-severe clinical activity and those with large or deep ulcers, to prevent complications (e.g. perforation, bleeding or obstruction).

R36 (**GPP**) Consider anti-tumour necrosis factor therapy early in the management approach, as a first-line option for both induction and maintenance, in people with severe gastrointestinal Behçets or in those with large/deep ulcers (to prevent complications such as perforation, bleeding or obstruction).

R37 (↑) Consider azathioprine or 6-mercaptopurine as a first-line option to prevent postresection clinical/endoscopic relapses, or perforation/bleeding in people with gastrointestinal Behçets.

R38 (↑↑) Offer* anti-tumour necrosis factor dose escalation and/or dose-interval reduction in resistant cases, to achieve clinical and endoscopic remission in people with gastrointestinal Behçets. Concomitant use of immunomodulators (e.g. azathioprine or 6-mercaptopurine) may achieve early and sustained clinical and endoscopic response.

R39 (↑↑) Offer* immediate surgery as a life-saving approach to people with gastrointestinal Behçets with uncontrolled bleeding, perforation or obstruction.

R40 (↑) Consider systemic corticosteroids and anti-tumour necrosis factor agents as a first-line option in people with gastrointestinal Behçets to avoid postresection clinical/endoscopic relapse.

R41 (**GPP**) Consider any other therapeutic option available in inflammatory bowel disease treatment protocols (e.g. ustekinumab or vedolizumab), in people refractory to all therapeutics available for gastrointestinal Behçets.

R42 (↑) Consider thalidomide as a last resort in people with gastrointestinal Behçets refractory to other available treatments. Combined treatment with an anti-tumour necrosis factor therapy may be an option for better outcomes. Mandatory monitoring, with neurophysiology and appropriate contraception and counselling in women and men patients of childbearing potential, is required.

Ocular

R43 (↑↑) Offer* oral/intravenous corticosteroids as a first-line option to treat sight-threatening eye disease in people with ocular Behçets. Topical corticosteroids may be coprescribed. Sight-threatening eye disease may be defined as one or more of the following features:

- clinically significant vitritis
- retinal infiltrate
- retinal vascular occlusion
- optic disc swelling
- macular oedema.

R44 (↑↑) Offer* a steroid-sparing agent (e.g. azathioprine, methotrexate or a calcineurin inhibitor) along with oral/intravenous corticosteroids for sight-threatening eye disease in people with ocular Behçets.

R45 (↑↑) Offer anti-tumour necrosis factor therapy as a second-line option to treat sight-threatening eye disease in people with ocular Behçets.

R46 (↑↑) Offer interferon-α-2a (if available) to treat sight-threatening eye disease in people with ocular Behçets.

R47 (↑↑) Offer tocilizumab to people with ocular Behçets who have not responded to anti-tumour necrosis factor or interferon-α-2a therapies.

R48 (↑) Only consider chlorambucil and cyclophosphamide as options to treat sight-threatening eye disease in people with ocular Behçets when biologic therapy has failed.

R49 (**GPP**) Manage non-sight-threatening eye disease in people with ocular Behçets depending on the frequency and severity of the episodes.

Θ There is insufficient evidence to recommend colchicine monotherapy in people with ocular Behçets.

Neurological

The following neuro-Behçets recommendations produced via a prior international neuro-Behçets consensus project[10] have been reviewed and adopted by the GDG.

General management of neuro-Behçets

R50 (**GPP**) Consider a neuro-Behçets diagnosis in people with neurological presentations in the context of other Behçets-defining features (recurrent oral or genital ulcerations, uveitis etc) or after the exclusion of other neurological conditions and disease mimics. Consider the international consensus recommendation (ICR) diagnostic criteria for neuro-Behçets in adults.[10] There are no corresponding criteria at present for children and young people.

R51 (**GPP**) When considering a diagnosis of neuro-Behçets take into account:

- the typical parenchymal presentation in people with suspected neuro-Behçets, namely subacute onset of brainstem syndrome, cerebral hemispheric syndrome, spinal cord syndrome or a combination of these, which can manifest through a multitude of signs/symptoms (including ophthalmoplegia, cranial nerve deficit, speech impairment, hemiparesis, hemisensory loss, myelopathy, sphincter symptoms, headaches, meningoencephalitis, encephalopathy, seizures, cognitive impairment, behavioural changes, etc), as well as its course (i.e. relapsing–remitting pattern or a primary or secondary progressive course)
- the nonparenchymal presentation in people with suspected neuro-Behçets who present with headaches and visual impairment secondary to intracranial hypertension, cerebral thrombophlebitis, cerebral vascular accident, arterial thrombosis, dissection or aneurysm, usually as a monophasic illness, although relapses can ensue
- that neuro-Behçets can present as a combination of parenchymal and nonparenchymal forms.

R52 (**GPP**) Consider the possibility that headaches in people with suspected neuro-Behçets are common and can occur during flare-ups, in the absence of central nervous system involvement. Investigate people with Behçets (e.g. brain magnetic resonance imaging and/or magnetic resonance venography and lumbar punctures), especially when headaches are severe or incapacitating, progressive, refractory or

persistent, or if they are related to visual or neurological symptoms and signs.

Investigations and assessment

R53 (**GPP**) Be aware that serological markers for inflammation (i.e. erythrocyte sedimentation rate and C-reactive protein) might be normal in people with suspected neuro-Behçets.

R54 (**GPP**) Perform magnetic resonance imaging including contrast, and magnetic resonance venography in people with suspected neuro-Behçets to investigate parenchymal disease and cerebral venous thrombosis, respectively, and to help inform the differential diagnosis.

R55 (**GPP**) Offer cerebrospinal fluid (CSF) examination in people with suspected neuro-Behçets to establish the diagnosis and exclusion of other pathologies. Note that parenchymal neuro-Behçets is usually associated with CSF pleocytosis, raised CSF protein and absence of oligoclonal bands; nonparenchymal neuro-Behçets is associated with elevated CSF pressure. However, a completely normal CSF does not exclude parenchymal neuro-Behçets.

R56 (**GPP**) Consider monitoring interleukin (IL)-6 cytokine serum and cerebrospinal fluid (CSF) levels in people with suspected neuro-Behçets. Elevated CSF IL-6 levels are an indicator of ongoing disease activity.

R57 (**GPP**) Avoid making a diagnosis based exclusively on asymptomatic neurophysiological findings in people with suspected neuro-Behçets.

R58 (**GPP**) Consider the modified Rankin scale[11] to measure the level of disability for people diagnosed with neuro-Behçets.

Treatments

There are no comparative studies on the treatment options for neuro-Behçets. The recommendations below are based on limited, lower-certainty evidence and GDG consensus.

R59 (**GPP**) Consider induction and maintenance treatments for people with neuro-Behçets, in line with other neuroinflammatory conditions. Be aware that patients may already be on immunosuppressive therapy due to systemic Behçets features and/or other organ system involvement.

R60 (↑↑) Offer* a course of high-dose intravenous corticosteroids to people in the acute form (first or relapsing attack) or those with the subacute form of parenchymal neuro-Behçets, followed by a maintenance dose of oral corticosteroids for up to 6 months. In the acute phase, the course of high-dose intravenous corticosteroids would enable significant disease suppression or induce remission.

R61 (↑↑) Offer* azathioprine alongside systemic corticosteroids to people with neuro-Behçets who have experienced parenchymal relapse or have had inadequate response to maintenance corticosteroids with ongoing systemic Behçets features. Other immunosuppressive alternatives include mycophenolate mofetil and methotrexate.

R62 (↑↑) Offer* cyclophosphamide or anti-tumour necrosis factor therapy combination as a first-line option in addition to high-dose intravenous corticosteroids, in the acute or subacute stage, to people with parenchymal neuro-Behçets with severe clinical manifestations or poor prognostic factors (i.e. at least one of the following: brainstem or spinal cord involvement and cerebrospinal fluid pleocytosis).

R63 (↑) Consider anti-tumour necrosis factor therapy early in the management of people with parenchymal neuro-Behçets and those with poor disease control (recurrent relapses or progression) or intolerable side-effects to immunosuppressive therapy.

R64 (↑↑) Offer* azathioprine and anti-tumour necrosis factor therapy (infliximab) alongside systemic corticosteroids as a first-line therapeutic option, to people with neuro-Behçets who have experienced a major parenchymal episode.

R65 (↑) Consider alternative anti-tumour necrosis factor therapies (e.g. switching from infliximab to adalimumab or etanercept) in people with refractory neuro-Behçets.

R66 (↑) Only consider interferon-α (if available) or anti-interleukin-6 agents, as alternative therapeutic options in carefully chosen cases, in people with parenchymal neuro-Behçets who are refractory to other disease-modifying immunosuppressive agents and anti-tumour necrosis factor (TNF) therapy, or if anti-TNF therapy is contraindicated.

R67 (↑↑) Offer* a course of high-dose intravenous corticosteroids to people with nonparenchymal cerebral venous thrombosis neuro-Behçets, followed by a maintenance dose of oral corticosteroids for up to 6 months.

R68 (↑) Consider azathioprine or anti-tumour necrosis factor therapy, in addition to oral corticosteroids over 6 months (tapering stage of steroids) to people with active systemic Behçets, recurrent nonparenchymal neuro-Behçets or a previous or concurrent parenchymal neuro-Behçets.

R69 (↑) Consider anti-tumour necrosis factor therapy to treat acute flares in people with nonparenchymal neuro-Behçets (e.g. cerebral venous thrombosis) in case of recurrence.

R70 (↑↑) Avoid* ciclosporin in people with a history of neuro-Behçets, due to potential neurotoxicity. If previously offered, ciclosporin should be stopped at the first indications of parenchymal neuro-Behçets involvement.

Θ There is insufficient evidence of benefit or harm to recommend routine use of anticoagulants in people with cerebral venous thrombosis neuro-Behçets. If using anticoagulants, exclude a systemic aneurysm prior to initiation.

Vascular

Arterial involvement

R71 (↑↑) Offer oral corticosteroids and cyclophosphamide pulses or anti-tumour necrosis factor (TNF) as an induction and maintenance therapy (minimum 2 years), comprising corticosteroids and azathioprine or continued anti-TNF, to people with aortic and peripheral arterial involvement associated with Behçets.

R72 (↑↑) Offer* stenting or surgery without delay to symptomatic people with aortic and peripheral arterial involvement associated with Behçets.

Pulmonary arterial aneurysm

R73 (↑↑) Offer* oral corticosteroids and cyclophosphamide or anti-tumour necrosis factor as a first-line option to people with pulmonary arterial aneurysm associated with Behçets.

R74 (↑) Consider tocilizumab or interferon-α-2a (if available) in people with pulmonary arterial aneurysm associated with Behçets with inadequate response to oral corticosteroids and cyclophosphamide or anti-tumour necrosis factor agents or if there are contraindications.

Deep-vein thrombosis

R75 (↑) Consider oral corticosteroids and/or anti-tumour necrosis factor (TNF) as a first-line therapy option in people

with acute, deep-vein thrombosis or severe/refractory venous thrombosis associated with Behçets, and maintain on anti-TNF or azathioprine therapy for a minimum of 2 years.

R76 (↓↓) Do not offer* anticoagulants alongside immunosuppressive therapy in people with deep-vein thrombosis associated with Behçets, as the risk of adverse events may exceed the benefits.

R77 (↑) Consider interferon-α-2a (if available) as a second-line option for achieving recanalization and preventing relapse in people with lower-extremity deep-vein thrombosis associated with Behçets.

R78 (**GPP**) Offer a high dose of oral corticosteroids and azathioprine to people who present with superficial phlebitis or deep-vein thrombosis and pyrexia of unknown origin as soon as possible after other conditions (e.g. infections) have been excluded and a Behçets diagnosis has been made. If the response to corticosteroids is not prompt, add tumour necrosis factor inhibitors.

Conception, pregnancy and breastfeeding

R79 (**GPP**) Manage pregnancies in women with Behçets in a multidisciplinary team setting, with both a physician and obstetrician with interests in rheumatology and perinatal medicine.

R80 (**GPP**) Offer pre-conception counselling to women with childbearing potential with Behçets to ensure optimization of their treatment or medication; in particular, advise them about contraception if they are taking thalidomide or mycophenolate mofetil.

R81 (**GPP**) Provide ultrasound assessment to monitor fetal growth.

R82 (**GPP**) Suggest that the decision about the mode of delivery should be made by the patient in consultation with their obstetrician. Caesarean section is not mandated but is often advised if there is concern about either genital ulceration or the development of pathergy.

R83 (**GPP**) Encourage breastfeeding in all women with Behçets. If medication has been used during pregnancy, then it is almost certainly safe for the mother and baby to take while breastfeeding.

Psychological

R84 (**GPP**) Include a clinical psychologist in the multidisciplinary team. People with Behçets should be screened and monitored routinely by all relevant healthcare professionals.

R85 (**GPP**) Provide general emotional support and consider focused interventions, if psychological distress is identified, to support self-management and coping. Consider 'Motivational Interviewing' and 'Solution-Focused Therapy' approaches to better understand and improve medication adherence based on individual presentation and patient preference.

R86 (**GPP**) Consider psychological formulation-based approaches via professional psychological practitioners, drawing upon cognitive behavioural therapy (CBT) and 'third- wave' CBT approaches (e.g. Acceptance and Commitment Therapy or Compassion-Focused Therapy), or a mindfulness-based approach. Other psychological interventions (e.g. Eye Movement Desensitization and Reprocessing Therapy) should be considered for more complex history or experiences of Behçets and/or its treatment. Systemic approaches may also be of benefit, for instance formulations and/or interventions that incorporate the wider systems around the patient (e.g. carers, family members, employment, education, social factors or wider healthcare service involvement).

R87 (**GPP**) Offer access to neuropsychological assessment and intervention to people who present with neurological symptoms related to Behçets.

Alternative therapies

Θ There is insufficient evidence to recommend alternative therapies for people with Behçets.

Future research recommendations

The following list outlines future research recommendations (FRRs).

FRR1 A national registry and biobanking to improve phenotyping and treatment outcomes in people with Behçets.

FRR2 Genotype–phenotype correlation studies to inform a targeted therapeutic approach to care for people with Behçets.

FRR3 Well-designed studies to support the use of psychological therapies in a population with Behçets.

FRR4 Well-designed studies to address the needs of children and young people with Behçets and their families and to determine the best approaches to support them from a psychosocial perspective.

FRR5 Clinical trials in children and young people with Behçets.

FRR6 Establish a minimum dataset for reporting Behçets in people of all ages, including quality of life and other outcome measures.

FRR7 Whole-exome sequencing to identify genotype–phenotype correlation in Behçets.

FRR8 Well-designed clinical trials to evaluate the efficacy and safety of neuro-Behçets treatments.

FRR9 Establish factors influencing the prognosis of neuro-Behçets.

FRR10 Randomized controlled trials to evaluate the safety and efficacy of oral Janus kinase inhibitors compared with appropriate interventions commonly used in people with Behçets.

4.0 Algorithm

The recommendations, discussions in the LETR (Appendix C), and consensus specialist experience were used to inform the algorithm/pathways (Figures 1 and 2).

5.0 Background

5.1 Definition

Behçets is named after a Turkish dermatologist, Hulusi Behçet, who in 1937 first reported a patient presenting with recurrent mouth and genital ulcers and uveitis.[8,12] We now know that Behçets occurs worldwide, but is most prevalent in Turkey (80–370 cases per 100 000) and Japan (13.5–35 per 100 000), followed by Korea, China, Iran, Iraq and Saudi Arabia.[13] It is a rare, multisystem, chronic and recurrent inflammatory condition that can affect blood vessels of any size and presents as multiple phenotypes.

In this guideline we will consider Behçets in all disease types and in people of all ages. Some lesions described in Behçets, such as aphthous ulceration, erythema nodosum and pseudoacne,

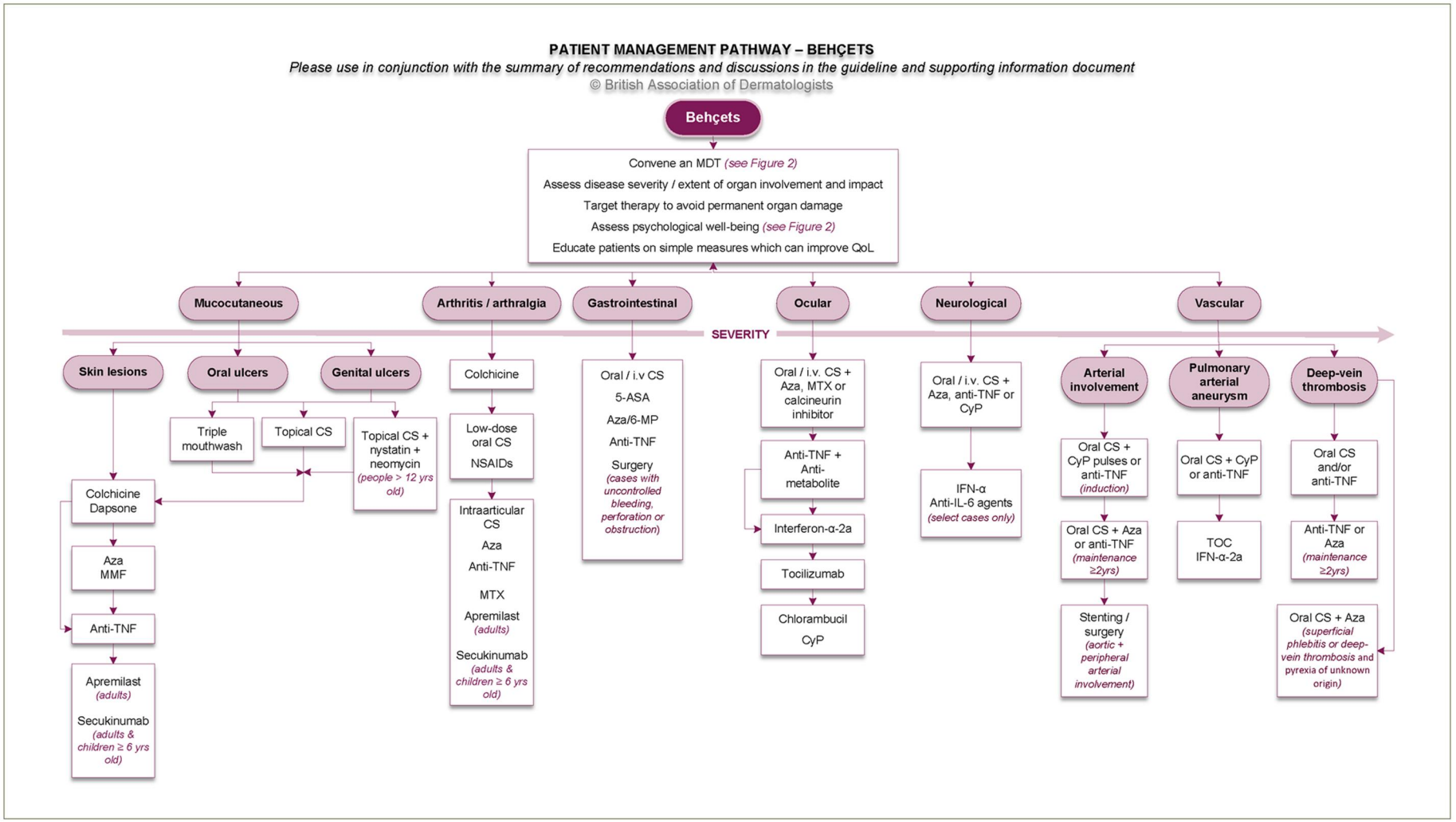

Figure 1. Management pathway for people with Behçets. For children and young people aged ≤ 16 years this should be within a specialist paediatric or adolescent centre. ASA, aminosalicylic acid; Aza, azathioprine; CS, corticosteroids; CyP, cyclophosphamide; IFN, interferon; IL, interleukin; MDT, multidisciplinary team; MMF, mycophenolate mofetil; MP, mercaptopurine; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; QoL, quality of life; TNF, tumour necrosis factor; TOC, tocilizumab

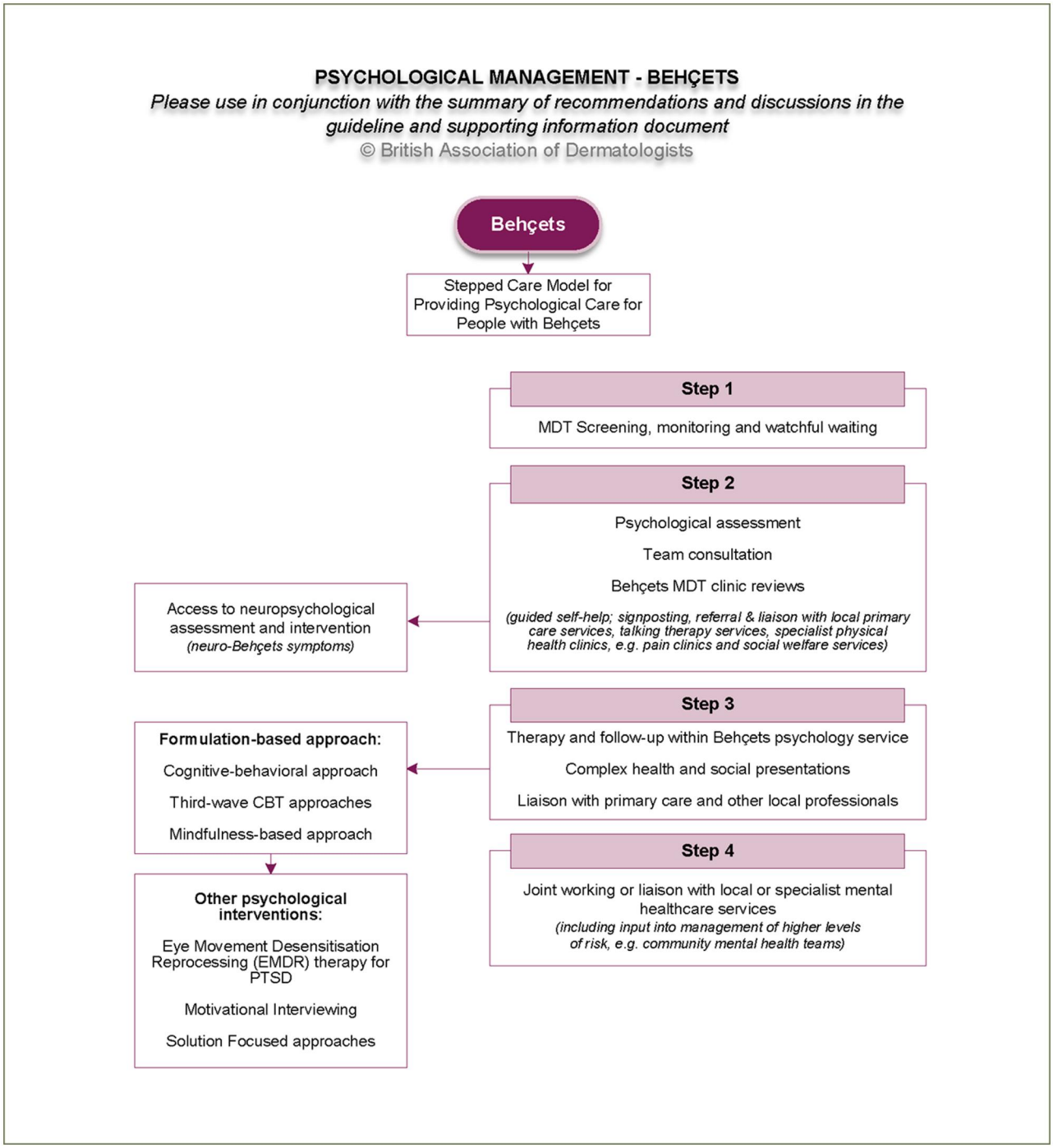

Figure 2. Stepped-care model for providing psychological care for people living with Behçets. CBT, cognitive behavioural therapy; MDT, multidisciplinary team; PTSD, post-traumatic stress disorder

may show inflammation without frank vasculitis on biopsy. The inflammatory skin conditions may be rather nonspecific, but associated with disease flares and malaise. Childhood onset of Behçets occurs, but disease prevalence and therapeutic interventions are reported mainly in adult populations.[14,15]

Presentation is often insidious, often without serological evidence of inflammation, contributing to both diagnostic challenge and delay. Typically, it is characterized by recurrent oral and genital ulceration, arthralgia, fatigue and skin symptoms. However, more acute presentations of inflammatory eye disease, and gastrointestinal, neurological and skin involvement can occur, potentially leading to blindness, permanent neurological injury or major blood vessel involvement.[16,17] This drives the need for increased diagnostic awareness in patients with a history of recurrent mucosal ulceration, and multidisciplinary input to aid prompt diagnosis and effective therapeutic intervention to prevent organ damage.

5.2 Epidemiology

Due to both the disease rarity and diagnostic difficulty, the true prevalence of Behçets is not known, but it appears to be highest along the 'Silk Route', stretching from the Far East to

the Mediterranean. In Western countries, such as the UK and USA, Behçets appears to be rarer.[15] A meta-analysis of epidemiological studies of adults with Behçets estimated a prevalence of 10.3 per 100 000 (95% CI 6.1–17.7), with higher rates in Turkey (119.8 per 100 000, 95% CI 59.8–239.9) than in the Middle East (31.8 per 100 000, 95% CI 12.9–78.4) and Europe (3.3 per 100 000, 95% CI 2.1–5.2).[17]

A recent, adult study in the Midwest of Ireland estimated the point prevalence of Behçets, based on the International Study Group (ISG) criteria, as 6.2 per 100 000 population.[18] A UK study in children aged < 16 years showed a 2-year period prevalence estimate of 4.2 per million (95% CI 3.2–5.4) and an incidence of 0.96 per million person-years (95% CI 0.66– 1.41). Male and female individuals are likely to be equally affected, but Behçets may present with different phenotypes in both childhood and adulthood.[8]

5.3 Aetiology

The pathology of Behçets remains unclear, but is believed to be an interplay between genetic and environmental factors. Numerous studies have identified an association with human leucocyte antigen (HLA)-B51 in multiple ethnic groups. More recently, an independent association within the major histocompatibility complex class I region has emerged.[17,19] A recent publication has suggested that an epigenetic interaction between HLA-B*51 and ERAP1 (endoplasmic reticulum aminopeptidase 1) may increase disease susceptibility.[20]

Common microbes such as herpes simplex virus and certain streptococcal species have been proposed to activate the immune system via heat shock proteins and activation of the T helper 17 and interleukin-17 pathways,[21] providing targeted routes for therapeutic intervention.

5.4 Phenotypic variation

In the UK, the mucocutaneous phenotype, with recurrent oral and genital ulceration and variable skin lesions, presents most commonly in people of all age groups including children.[8] The reported skin lesions are variable and include erythema nodosum, pseudofolliculitis, superficial thrombophlebitis and neutrophilic dermatoses. Male patients have been reported to present with papulopustular skin lesions, in contrast to female patients, who are more likely to present with erythema nodosum (septal panniculitis)-type skin lesions.[16]

The QoL of these patients has been significantly reduced, and patients often report fatigue, pain and loss of energy.[22] However, there have been no QoL studies in children and young people. Gastrointestinal involvement with ulceration is reported more commonly in patients from Korea and Japan. Generally, the skin pathergy test is considered to be both sensitive and specific within Mediterranean and Middle Eastern countries, as well as Japan, but the rate of a positive response from the test appears to be declining in some countries.[16] This may also reflect a decline in its general clinical application.

5.5 Diagnosis

Diagnosing Behçets remains a challenge as there are no diagnostic biomarkers or genetic tests. Instead, diagnosis relies on affected individuals meeting prespecified published clinical criteria and the exclusion of disease mimics. Behçets often evolves gradually, meaning that affected individuals may present with an incomplete phenotype lasting for many years. This natural disease progression challenges the sensitivity and specificity of published diagnostic criteria and presents a clinical challenge to prompt diagnostic accuracy and effective therapeutic intervention.

The most widely cited diagnostic criteria are the ISG criteria (1990) and the International Criteria for Behçet's Disease (ICBD; 2006, revised 2013). The ISG suggests that recurrent oral ulceration is essential to make a diagnosis of Behçets, along with any two of the remaining four items (genital ulcers, skin involvement, eye involvement or positive pathergy test),[22] while the ICBD weighs oral ulceration and genital ulcers more heavily than other items, but does not make them essential. The ICBD also includes vascular manifestations, which the ISG does not. The ICBD criteria have proven to be more sensitive, but less specific than the ISG criteria.[21] In children, paediatric criteria also exist and ISG and ICBD may not perform as well as in adults with Behçets.[14,23]

As the diagnosis of Behçets depends on criteria fulfilment, full diagnosis may not be possible at the initial presentation. This is more pronounced in the recently designed Korean Study Group's GIBD diagnostic set.[24] Therefore, patients with recurrent, mucocutaneous sign(s) and symptoms should continue with follow-up to confirm diagnosis and assess disease impact and progression.

5.6 Differential diagnoses

Behçets presents with many phenotypes, which lends itself to a wide-ranging differential diagnosis (Table 2). The history of recurrent orogenital ulceration is a helpful guide to diagnosis but does not always capture individuals with incomplete disease. Recently described mimics of Behçets include monogenic autoinflammatory diseases such as haploinsufficiency A20.[25] In children, the PFAPA syndrome (periodic fever, aphthous ulceration, pharyngitis, adenitis) is an important differential, particularly in those with fever.[26] As the presence of aphthous ulcers is a key diagnostic feature in Behçets, conditions associated with aphthous ulceration are particularly important to exclude, such as idiopathic recurrent aphthous and genital ulceration, inflammatory bowel disease, coeliac disease, seronegative arthropathies, haematological malignancies, Sweet syndrome and systemic lupus erythematosus.[27]

5.7 Organ involvement management and treatment hierarchy

The GDG set out to provide an up-to-date, holistic and evidence-based approach to optimize the management of people with Behçets. By definition, people with Behçets will have more than one organ affected by disease and this can make therapeutic intervention challenging. However, switching off inflammation in the affected organs is made easier as the selected agent is likely to work at multiple sites. Disease may be severe, with organ damage, particularly if there is ocular and/or neurological involvement leading to significant morbidity and mortality.

The degree of disease activity in any organ will direct treatment choice and may be used to characterize the phenotype (e.g. neuro-Behçets, mucocutaneous Behçets). While this guideline covers multiple specialties, the nature of Behçets is such that multiple sites are often affected in disease flares and simultaneously settle during remission. This means that systemic therapies are often indicated and will show efficacy across several organs as the inflammation settles. In the short term, this therapy will often be systemic CS, either intravenously or orally. Similarly, for longer-term control, to reduce disease flares, the same steroid-sparing systemic agents will

Table 2. Main differential diagnoses

Organ/system and specific feature	Histology and investigations	Differentials
Skin		
Erythema nodosum-like lesions	More common in female than male patients Inflammatory perivascular infiltrate can be seen, unlike in other types of erythema nodosum They present as either lobular or mixed septal and lobular panniculitis	Other causes of panniculitis
Papulopustular lesions	Sterile pustules, pseudofolliculitis, acne-like lesions	Acne vulgaris Folliculitis Furuncles
Neutrophilic dermatoses	Increased neutrophilic infiltrate seen (pyoderma gangrenosum is a diagnosis of exclusion with no specific histological features)	Idiopathic Sweet syndrome and pyoderma gangrenosum
Mucosal ulceration		
Aphthous oral ulcer (recurrent aphthous stomatitis)	Recurrent and painful ulcers affecting the mucosal surface of the lips, soft palate, buccal mucosa and tongue. These may be minor or major (heal with scarring)	Idiopathic recurrent aphthous ulcers Aphthous ulcers associated with inflammatory bowel disease
Aphthous genital ulcer	Recurrent and painful ulcers; the labia minora and majora are the most commonly affected sites in female patients The scrotum and perianal area are the most commonly affected sites in male patients	Idiopathic recurrent aphthous ulcers Aphthous ulcers associated with inflammatory bowel disease
Ocular		
Anterior uveitis	Granulomatous vs. nongranulomatous keratic precipitates The bulk of inflammation is seen anterior to the crystalline lens	Idiopathic uveitis Chronic anterior uveitis: anterior uveitis is not a classic defining ocular finding in Behçets, but can be supportive
Intermediate uveitis	The bulk of inflammation is seen behind the crystalline lens and anterior to the retina Significant inflammation can be seen within the vitreous in the context of an inflammatory retinal vein occlusion	Intermediate uveitis is not a classic defining ocular finding in Behçets, but can be supportive
Posterior uveitis	The bulk of inflammation is within the retina or choroid Inflammatory retinal vein occlusions resemble a traditional retinal vein occlusion but can be multifocal and occur in the presence of intraocular inflammation. While retinal vein occlusions occur commonly in the general population, they are typically a sign of cardiovascular disease and occur in the older population Retinal infiltrates may occur within the inner retina and cause irreversible retinal destruction. Infiltrates may be confused with an infectious aetiology. Common intraocular infections should be excluded including toxoplasmosis, tuberculosis and syphilis	Both inflammatory retinal vein occlusions and retinal infiltrates are a common ocular finding in Behçets
Scleritis and episcleritis	Focal or diffuse redness of the sclera or episclera are usually associated with pain or discomfort Other inflammatory causes should be excluded. Both infections and inflammatory diseases of collagen can cause scleritis or episcleritis	While scleritis and episcleritis are reported in Behçets, they are not commonly thought of as disease-defining events
Neurological		
Brainstem presentation	Neuro-Behçets can be differentiated from its mimics by a combination of characteristic clinical and paraclinical neurological findings in addition to the associated systemic features	Multiple sclerosis, stroke affecting younger people (< 45 years of age), intracranial hypertension, meningoencephalitis and myelitis
Myelitis	Spinal cord intrinsic signal change	Multiple sclerosis
Meningoencephalitis	CSF pleocytosis (neutrophils and lymphocytes) and raised CSF protein, usually absent oligoclonal bands	Infectious or other inflammatory causes of meningoencephalitis

(continued)

Table 2. (continued)

Organ/system and specific feature	Histology and investigations	Differentials
Venous sinus thrombosis	Venous drainage obstruction on venography	Other neuroinflammatory conditions, antiphospholipid syndrome
IIH (secondary IIH)	Raised CSF pressure	Idiopathic or primary IIH
Vascular		
Arterial aneurysm	Abnormal imaging: computed tomography angiography, MRI angiography, conventional angiography or ultrasound, showing aneurysms Echocardiography	Takayasu arteritis Atherosclerosis Treponemal infection Ehlers–Danlos syndrome Marfan syndrome Turner syndrome Familial thoracic aortic aneurysms
Deep-vein thrombosis	Abnormal duplex venous ultrasonography with obstruction Venous drainage obstruction on venography Elevated D-dimer Factor V Leiden	Prothrombotic clotting disorder Prolonged inactivity Chemotherapy Pregnancy Obesity
Gastrointestinal		
Typically local, solid, single or a few ileocecal ulcers on endoscopy. Right-lower-quadrant pain is more frequent and/or prominent than diarrhoea	Mostly ileocecal, isolated, solid (≥ 1 cm) single or a few (2–5) segmental ulcers. To a lesser extent, small aphthous ileocecal or colonic rather segmental ulcers High complication potential (perforation, bleeding), up to 30% or more, based on ulcer morphology (nonaphthous, large, volcano-type deep ulcers are accepted as prone to complication) Involvement of upper parts of GI tube (i.e. oesophageal and gastric) is very rare and could not be accepted as GI Behçets, unless it could not prove as viral (cytomegalovirus, herpes simplex virus), acid-related peptic ulcer or GERD related Diagnosis of GI ulcer (typical or atypical) may be time dependent and considered as definitive, suspected and probable according to the Behçets diagnostic criteria Histopathology rarely reveals vasculitis in standard mucosal punch biopsies (frequent sampling inadequacy, tissue insufficiency and rapidly smouldering tendency of typical early-stage signs of vasculitis)	Crohn disease GI tuberculosis Monogenetic IBDs: e.g. interleukin-10 deficiency, XIAP deficiency, chronic granulomatous disease (only 10% after the age of 18 years) Myelodysplastic syndromes (trisomy 8 +) NSAID-related aphthous GI lesions Granuloma formation found during histopathological examination may be an indicator of either coeliac disease or GI tuberculosis After resection, very early aggressive endoscopic recurrence at anastomosis may be a consequence of an ongoing inflammation at the time of the surgery and is commonly seen in GI Behçets. In treatment-resistant cases this condition may end with mandatory stoma Perianal fistula is a common indicator for coeliac disease. It is either very rare or coincidental in GI Behçets and GI tuberculosis Development of enteroabdominal fistula may arise from either ongoing inflammation or pre- or postsurgical care following bowel resection in both GI Behçets and coeliac disease

CSF, cerebrospinal fluid; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IBD, inflammatory bowel disease; IIH, increased intracranial hypertension; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; XIAP, X-linked inhibitor of apoptosis protein.

often be used for different body sites. Treatment aims to improve the QoL and prevent end-organ damage, such as blindness, cerebrovascular damage and organ perforation.

Systemic CS, intravenous or oral, are often a first-line choice to induce remission for severe disease flares. To maintain remission and spare CS, other systemic agents are then used. The drug selection is directed by therapeutic efficacy according to the most vulnerable organ, with primacy given to ocular, neurological or visceral involvement. For mucocutaneous disease, which is the commonest type presenting in the UK, targeted topical therapies may suffice, but for ongoing disease impacting QoL, systemic agents may be needed.

5.8 Paediatrics

Around 20% of people with Behçets will present in childhood.[28] The mucocutaneous phenotype is the most common, whereas vascular and neurological involvement are rare.[8] The performance of classification and diagnostic criteria for Behçets may not be as good in children, and further classification criteria for paediatric disease have been developed, known as PEDBD.[23] Features such as musculo-skeletal and GI involvement appear more frequently in children than in adults, and are not included in the commonly used criteria for Behçets including ISG, ICBD or PEDBD.[28] However, a preliminary study has observed a slightly more favourable accuracy of ICBD over PEDBD.[29]

The differential diagnoses in paediatric patients are similar to those in adults, but early age of onset may be indicative of a monogenetic mimic, or PFAPA.[26,28] PFAPA is a noninherited periodic fever syndrome with high fever lasting 3–7 days associated with the above symptoms, which reoccurs every 3–8 weeks. Monogenic autoinflammatory diseases can present as a Behçets phenotype, including haploinsufficiency A20.[30]

Evidence from clinical trials for treatment of Behçets in children and young people is extremely limited, and evidence is extrapolated from adult trials with adjustments to dosing as per trials for other conditions.

Because of the differences in presentation, differential diagnosis and drug dosing, Behçets in children and young people should be managed in a developmentally appropriate service, including access to an MDT with paediatric expertise. This is to ensure that health, education, social and psychological needs are addressed to lessen the impact of Behçets in this population.

Transition to developmentally appropriate adult services should be well planned and follow National Institute for Health and Care Excellence guidance. The NCEPOD (National Confidential Enquiry into Patient Outcome and Death) report[31] of transition from child to adult healthcare services also provides important information and resource. Tools such as Ready Steady Go[32] can facilitate the transition process. A person-centred approach should be followed, and transfer to adult services should be at a time that is right for the individual rather than being based on any age threshold.

5.9 Genetics

While Behçets is a complex (polygenic) disease (see Section 5.6), monogenetic inborn errors of immunity may present initially with features mimicking Behçets. This is highlighted by, but not limited to, haploinsufficiency of A20.[30,33] An extensive review identified 12 monogenetic mimics,[34] but increasingly others are being described, including the recent identification of DEX (deficiency of ELF4, X-linked), caused by loss-of-function mutations in *ELF4*.[35] As a result, next-generation sequencing (NGS) involving gene panels, whole-exome sequencing or whole-genome sequencing are used increasingly in the diagnostic investigations for Behçets. One advantage of this approach is that whole- exome or whole-genome sequencing can also provide the HLA-B51 status, as well as excluding a monogenetic Behçets mimic. Early disease onset, positive family history or atypical presentation constitute 'red flags' that should prompt clinicians to consider NGS, if available. That said, adult patients may also have monogenetic inborn errors of immunity, and thus could also benefit from NGS even with a presentation of Behçets later in life.

5.10 Psychological difficulties in Behçets

People with Behçets can experience a range of psychological difficulties, with depression and anxiety identified as the most prevalent,[36] and at higher rates than in the overall population.[37] Psychosocial distress and impact on QoL are associated with severity and duration of illness;[38,39] however, this association remains to be better understood.

Immune system flaring symptoms can be highly psychologically challenging due to their remitting–relapsing nature. Persistent fatigue and pain are frequently reported symptoms that are associated with anxiety, depression and reduced QoL.[36] Therefore, Behçets can impact negatively at personal and systemic levels, such as independence,[40] social roles,[41] ability to eat or maintain pleasure from eating, sexual functioning and body image,[42,43] family planning[44] and employment.[45]

The journey to Behçets diagnosis can also be long, uncertain, isolating and stressful, with the potential for experiences of misdiagnosis and extended periods without treatment. Involvement of sexual health clinics can be distressing due to the misdiagnosis of sexually transmitted infections relating to genital ulceration, along with the disruption this causes within relationships.[46]

Cognitive functioning can be impacted, particularly during episodes of flare-ups, in both Behçets and neuro-Behçets, typically impacting visuospatial function, processing speed, working memory, encoding and retrieval attention, and executive functioning.[47] Disease-related cognitive impairments are associated with anxiety and depression.[48]

Health-related QoL shows significant improvements with disease treatment.[36,39] Overall, a comprehensive understanding of the psychological and psychosocial challenges faced by those with Behçets is essential for providing appropriate support and care.

6.0 Recommended audit points

Current practice now recommends that all patients with Behçets are managed in age-appropriate, multidisciplinary teams at both diagnosis and review. Patients included in this audit are expected to be drawn consecutively from these clinics and, ideally, should be a minimum of 20 or all those reviewed in the last 12 months.

The audit points are summarized, with an expected 100% compliance:

1) All patients are clinically assessed in a multidisciplinary team appropriate to age and development.
2) The diagnostic criteria are documented in the notes and are in line with the 1990 ISG or ICBD diagnostic criteria.
3) At diagnosis and each follow-up visit, disease extent is recorded by a systems enquiry leading to site- specific examination for involvement of the following systems:
   - mucocutaneous (oral, genital and skin)
   - gastrointestinal
   - rheumatological
   - ocular
   - neurological
   - psychological.
4) An assessment of overall disease activity is made using a physician's and patient's global assessment, or a Behçets-specific disease activity tool.
5) Evidence that drug therapy is titrated to disease activity and made as a joint decision with the patient.
6) Assessment of disease impact is made using a quality-of-life assessment tool at diagnosis and each follow-up visit.
7) Patients are provided with a PIL about Behçets at diagnosis.

Appendix N (see Supporting Information) includes the set of audit standards, data items and data collection methodology.

7.0 External review: stakeholder involvement and peer review

The draft manuscript and the Supporting Information were made available to the memberships of the BAD and BSR and to the British Dermatological Nursing Group, Primary Care

Dermatology Society, Association of British Neurologists, Royal College of Ophthalmologists, British & Irish Society for Oral Medicine, British Society for Sexual Medicine, Royal College of Surgeons of England, Vascular Society of Great Britain and Ireland, British Society of Gastroenterology, Association of Clinical Psychologists UK, Royal College of Obstetricians and Gynaecologists, Royal College of Paediatrics and Child Health, and Behçet's UK.

All comments were actively considered by the GDG, and the guideline was updated, where appropriate. Following further revision, the finalized version was signed off by the BAD's Therapy & Guidelines Subcommittee and the BSR's Guidelines Steering Group, prior to submission for publication.

Upon publication in peer-reviewed journals the guideline will also be freely available to access from the BAD and BSR websites.

8.0 Limitations of the guideline

This document has been prepared on behalf of the BAD and BSR and is based on the best data available at the time of writing. It is recognized that under certain conditions it may be necessary to deviate from the guideline and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to this guideline should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence. The systematic review was limited to publications in English; this was a pragmatic decision, but the authors recognize this may exclude some important information published in other languages.

9.0 Plans for guideline revision

The proposed literature surveillance will be scheduled at ≤ 6 months, with a view to publish (in the absence of a trigger) appropriate updates 12 months after publication of the previous guideline iteration.

All recommendations will be treated as living. The literature surveillance may lead to amendments in some recommendations and/or the addition of new recommendations, requiring issuance of the next iteration of this living guideline.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix A Living systematic review protocol.

Appendix B Forest plots.

Appendix C Linking Evidence To the Recommendations (LETR):

- Relative values of different outcomes
- Balance between desirable and undesirable effects
- Certainty of evidence
- Patient values and preferences
- Cost
- Other considerations
- List of recommendations.

Appendix D GRADE profiles.

Appendix E Summary of included systematic reviews.

Appendix F Summary of comparative studies included in quantitative and qualitative synthesis.

Appendix G Narrative findings from noncomparative studies.

Appendix H PRISMA flow diagram.

Appendix I Critical appraisal of included systematic reviews—AMSTAR 2.

Appendix J Risk-of-bias analysis.

Appendix K Excluded studies.

Appendix L Methodology.

Appendix M Search strategy.

Appendix N Audit standards, data items and data collection.

Appendix O List of clinical trials registered on ClinicalTrials.gov.

Data availability

The data are available in the Supporting Information.

Funding sources and editorial independence

Development of this guideline has been funded independently by the British Association of Dermatologists (BAD). No external factors have detracted from BAD's organizational and editorial independence. The BAD has a strict adherence to its Sponsorship Policy and Principles.

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The following interests were declared over the duration of the guideline development:

RM is member of an advisory board for Janssen (nonspecific). **RJM** is (i) a member of advisory boards for AbbVie, Chugai, Novartis, Pfizer and Roche (specific); (ii) a speaker at international meetings funded by Chugai/Roche, Eli Lilly and Pfizer (specific); (iii) a director for the National Centre for Behçets Syndrome (specific); (iv) a chief investigator for the BioBehçet's trial (NIHR EME grant) (specific); and (v) a grant holder and chief investigator for the phase II trial 'Secukinumab in Behçet's', with funding provided to Liverpool University Hospitals NHS Trust (specific). **PB** (i) receives consultancy or lecturing fees from Sobi, Novartis and Roche (nonspecific); (ii) is a local principal investigator for the EMERALD trial (Sobi) (nonspecific); (iii) is chief investigator of the KDCAAP trial (nonspecific); and (iv) is a trustee of a patient-led charity for Kawasaki disease (nonspecific). **AFÇ** (i) participates on advisory boards and talks at meetings for irritable bowel disease funded by AbbVie, MSD, UCB Pharma, Takeda, Pfizer, Centurion, Janssen and Mgen (specific); (ii) is head of the Turkish IBD Association, which receives annual funding from MSD, AbbVie, Takeda, UCB Pharma, Centurion, Mgen, Pfizer and Janssen (specific); and (iii) receives funding to their clinic from MSD, AbbVie, Takeda, UCB Pharma, Centurion, Mgen and Janssen, which provides medical equipment used for Behçets (specific). **SSK** (i) is chairperson for Janssen (nonspecific); (ii) received speaker fees from LEO Pharma, Janssen and L'Oreal (nonspecific); and (iii) has a salary partly funded by a grant

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