**Guideline for Diagnosis and Management of Hairy Cell Leukaemia (HCL) and Hairy Cell Variant (HCL-V)**

**A British Society for Haematology Guideline**

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**Methodology**

This guideline was compiled according to the BSH process at

https://b-s-h.org.uk/guidelines. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at <http://www.gradeworkinggroup.org>.

***Literature review***

Literature search was undertaken by Niche Science and Technology Ltd on 30th June 2018, using PubMed, with a further check by the authors on 1st March 2020. The following search terms were used; hairy cell leukaemia AND; *BRAF* V600E mutation, vemurafenib, dabrafenib, immunotherapy, rituximab, immunotoxin conjugate, moxetumomab, minimal residual disease, hairy cell leukaemia variant.

***Review of the manuscript***

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee Haemato-Oncology Taskforce, the BSH Guidelines Committee and the Haemato-Oncology Sounding Board of BSH. It was also placed on the members section of the BSH website for comment, and has been reviewed by the Leukaemia Care patient advocacy group.

**Introduction**

Hairy cell leukaemia (HCL) is an uncommon, chronic B-cell leukaemia, first reported as a distinct entity in the 1950s (1, 2). HCL accounts for 2% of lymphoid leukaemias, with a male predominance, and median age at diagnosis of 58 years. Classical HCL and its variant form (HCL-V) are now regarded as separate entities(3) with different cytological, haematological and immunophenotypic features. *BRAF* V600E mutation, present in virtually 100% of cases of classical HCL(4) is regarded as a disease-defining event, and is absent in HCL-V.

Advances in management of classical HCL, from use of interferon in the 1980s, to purine analogues in the 1990s, monoclonal antibodies in the 2000s and BRAF inhibitors in the current decade have resulted in excellent prognosis, with the majority of patients achieving long lasting remissions and prolonged survival (5, 6). There remains no clear optimal treatment for HCL-V, which is one tenth as common as classical HCL, with a 5 year survival rate of 57%(7). Advances in diagnostics and treatment necessitate an update of the 2012 BSH guideline (8).

**Clinical and Laboratory Features**

Some patients with HCL are asymptomatic, with incidental finding of pancytopenia. Others present with lethargy, or infection. Symptomatic splenomegaly is unusual, although the spleen is frequently palpable.

Cytopenias, normally affecting at least two lineages are a consistent laboratory feature. Leucopenia is a frequent feature in classical HCL, monocytopenia is virtually always present. Contrastingly, monocytopenia is not a feature of HCL-V, where there is often a leucocytosis. Classical hairy cells may be seen in the peripheral blood film (see description below).

Table 1: Summary of the main clinical and laboratory features of classical HCL at diagnosis(8)

|  |  |
| --- | --- |
| **Feature** | **Prevalence** |
| Palpable splenomegaly | 60-70% |
| Palpable hepatomegaly | 40-50% |
| Abdominal lymphadenopathy on CT\* scan | 10% |
| Haemoglobin <100g/l | 70% |
| Platelet count <100 x 109/l | 80% |
| White cell count <5 x 109/l | 65% |
| Neutrophils <1 x 109/l | 70% |
| Monocytes <1 x 109/l | >90% |
| Hairy Cells in blood film | 95% |

\*Computed tomography

**Diagnostic Tests**

Blood Film, Classical HCL

The peripheral blood film may show characteristic medium-sized lymphoid cells with an oval or indented (kidney-shaped) nucleus with homogenous, ground-glass chromatin, slightly less clumped than that of a normal lymphocyte. The nucleolus is typically absent, or inconspicuous. Cytoplasm is abundant and pale blue, with circumferential ‘hairy’ projections (9). Discrete cytoplasmic vacuoles or rod-shaped inclusions (ribosome lamellar complexes) may be seen(3).

Bone Marrow Aspirate and Trephine Biopsy

Bone marrow aspiration is frequently unsuccessful, reflecting fibrosis induced by the hairy cell infiltrate. The bone marrow trephine biopsy often shows patchy infiltration, making it important to obtain a good-sized specimen. The hairy cell infiltrate is characterised by widely spaced lymphoid cells, and the pattern of marrow involvement is commonly interstitial, becoming diffuse, creating a ‘honeycomb’ appearance. ‘Blood lake’ pseudo-sinus formation may be seen, with extravasation of red cells into involved areas. Reticulin fibrosis may be present, but collagen deposition is not seen. There may be a minor intra-sinusoidal component.

Of note, there are cases displaying a hypocellular marrow, where loss of haemopoietic elements, in particular of the granulocytic lineage, can lead to an incorrect diagnosis of aplastic anaemia. Immunohistochemical demonstration of an abnormal B-cell infiltrate is essential in these cases, in which the hairy cell infiltrate may be almost invisible on routine stains(3).

Immunophenotyping by Flow Cytometry (FC) and Immunohistochemistry (IHC)

The classic immunophenotypic profile of HCL consists of bright surface immunoglobulin of multiple clonally related isotypes (10, 11); bright co-expression of CD20, CD22 and CD11c; and expression of CD103, CD23, CD123, TBX21 (TBET), annexin A1, FMC7, CD200 and cyclin D1(3). Annexin A1 is the most specific marker; it is not expressed in any other B-cell lymphoma (12) and can be useful to distinguish classical HCL from HCL-V, and from splenic marginal zone lymphoma.

If liquid marrow is available for FC, the ‘Hairy Cell Panel’ of CD11c, CD25, CD103 and CD123 (13) can be useful to distinguish HCL (score 3-4) from other B- cell disorders (score 0-1). Further markers such as CD27, CD43, CD81 and CD200 may be differentially expressed in HCL and HCL-V, reflecting their differing disease biology, and may be informative when included in flow cytometry panels (14). CD27 and CD38 are typically negative in classical HCL which distinguishes it from other lymphoproliferative disorders (15).

IHC panels for use on the marrow biopsy may include CD20, DBA44, Annexin A1, CD25 and Cyclin D1 (16). Cytochemistry for tartrate-resistant acid phosphatase (TRAP) has been replaced by TRAP IHC, and IHC for the V600E-mutant BRAF protein is also available. Both cyclin D1 and SOX11 are expressed in a significant proportion of HCL cases, which appears highly specific for HCL outside of mantle cell lymphoma (17).

Spleen histology

Need for diagnostic or therapeutic splenectomy is infrequent, but when undertaken, histology shows diffuse expansion of the red pulp, with disruption of normal architecture, and extreme atrophy of the white pulp.‘Blood lakes’ surrounded by neoplastic cells may be seen. These appearances are shared by HCL-V and splenic diffuse red pulp small B cell lymphoma (SDRPL), included as a provisional entity in the current WHO Classification (3).

Differential Diagnosis

The differential diagnosis of HCL includes other lymphoid malignancies which present with splenomegaly, including the B cell neoplasms: hairy cell leukaemia variant (HCL-V), lymphoplasmacytic lymphoma (LPL), splenic marginal zone lymphoma (SMZL), B- cell prolymphocytic leukaemia (B-PLL) and splenic diffuse red pulp small B cell lymphoma (SDRPL), and the T-cell neoplasms: T cell large granular lymphocytic leukaemia (T-LGL) and hepatosplenic T-cell lymphoma. Useful differentiating factors are described in Table 2.

Myeloid disorders presenting with pancytopenia, splenomegaly and bone marrow fibrosis also form part of the clinical differential diagnosis.

Table 2: Differential Diagnosis of Classical Hairy Cell Leukaemia

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **HCL** | **HCLv** | **SDRPL** | **SMZL** |
| **Gender M:F** **Age** | 4:1 Median: 58 years | M>F Middle aged- elderly | 1:1>40 years | 1:1>60 years |
| **Cells in peripheral blood** | Hairy cells with circumferential hairy projections (may be infrequent). | Hairy cells with variable cytoplasmic projections. Prominent nucleoli. | Polar cytoplasmic projections. Basophilic cytoplasm. | Villous lymphocytes with polar cytoplasmic projections.  |
| **Immunophenotype** | CD20 bright +CD103+CD25+CD27-CD11c+CD123+DBA44+Annexin A1+Cyclin D1+ (weak) | CD20 bright+CD103+CD25-CD27+CD11c+CD123-DBA44+Annexin A1-Cyclin D1- | CD20 bright+CD103-/+CD25-CD27+CD11c-/+CD123-DBA44+Annexin A1-Cyclin D1- | CD20+CD103-CD25-/+CD27+CD11c+/-CD123-DBA44+Annexin A1-Cyclin D1- |
| **Marrow involvement** | Diffuse and interstitial ‘honeycomb’ pattern. Minor intrasinusoidal component may be seen. Fibrosis marked. | Interstitial, rarely diffuse. Predilection to sinusoidal infiltration. Reticulin fibrosis not significant (easier to aspirate than classical HCL).  | Intrasinusoidal, interstitial and nodular. | Nodular and intrasinusoidal. |
| **Spleen histology** | Red pulp infiltration with red blood cell lakes. Atrophic white pulp. | Red pulp infiltration with red blood cell lakes. Atrophic white pulp. | Diffuse red pulp involvement of cords and sinusoids. White pulp spared. | Marked expansion of white pulp and infiltration of red pulp. |
| **Molecular genetics** | *BRAF* V600E mutated in most cases.  | *BRAF* V600E not mutated. *MAP2K1* mutations. | *CCND3* PEST domain mutations. | Del7q (40%), *NOTCH2* and *KLF2* mutations. |

Molecular Genetics

The *BRAF* V600E mutation was identified, in 2011, using whole-exome sequencing, as the causal genetic event in the pathogenesis of HCL (4). The mutation confers constitutive *BRAF*-MAPK pathway activation and favours tumour survival. *BRAF* V600E has also been proposed to explain the ‘hairy’ morphology, possibly via overexpression and constitutive activation of the RHO family of small GTPases and upregulation of GAS7 (a growth arrest-specific molecule) (18).

Although *BRAF* V600E mutation testing may not always be necessary for the diagnosis of HCL, mutation analysis is useful when faced with diagnostic uncertainty, and early identification of *BRAF* V600E allows more precise monitoring when disease-eradicating therapies are used. Various methodologies are in use for detection (19) . Next Generation Sequencing (NGS) may become the preferred methodology in the longer term (20).

Classical HCL typically has no biased use of specific IGHV and expresses IGHV with mutated conformation (10, 11, 21). However, a minor subset, with classical HCL phenotype and unmutated IGHV has been described. This subset often has leucocytosis at presentation, is refractory to single-agent cladribine, has a more aggressive behaviour and can harbour *TP53* mutations (22).

Conversely, HCL-V frequently uses IGHV4-34 in unmutated conformation (approximately 40% of all HCL-V). This group typically has higher disease burden at diagnosis, poor response to single-agent cladribine and shorter overall survival (23). Whole-exome sequencing of these HCL-V cases has identified *BRAF* V600E mutation to be lacking, with *MAP2K1* the most frequently mutated gene, encoding MAP2K1/MEK1 downstream from *BRAF*(24), a potential future therapeutic target (25).

Additional recurrent mutations have been identified in HCL, including *CDKN1B* (p27) (26).

**Staging and Indications for Treatment**

There is no widely agreed staging system for HCL. The disease affects mainly bone marrow and spleen, with lymphadenopathy in a minority. Approximately 9% of patients have abdominal lymphadenopathy at presentation and the incidence increases at relapse. Lymphadenopathy has been associated with inferior response to treatment and reduced overall survival (OS) (27). While computerized tomography (CT) at presentation is not considered essential, it may provide some prognostic information. Where lymphadenopathy has been demonstrated, response assessment should include a repeat CT.

In cases where cytopenias are minimal, and the patient largely asymptomatic, an initial period of watchful waiting is usually appropriate, but the majority of patients are symptomatic, with anaemia, infections or bleeding, or symptomatic splenomegaly, justifying treatment.

It is good practice to ensure patients are directed to additional services for support following diagnosis. The rarity of the condition can contribute to a patient’s distress and many patients may not have a full understanding of their condition. Active monitoring can be particularly challenging psychologically, and the concept of a lifelong illness may be overwhelming for some patients.  Charitable organisations provide advice, information and support to HCL patients at any stage of their diagnosis and beyond.

Leukaemia Care: <https://www.leukaemiacare.org.uk/support-and-information/>

Blood Cancer UK: <https://bloodcancer.org.uk/understanding-blood-cancer/>

Cancer Research UK: <https://www.cancerresearchuk.org/about-cancer/hairy-cell-leukaemia/living-with>

NHS Local Cancer information and support services: <https://www.nhs.uk/service-search/other-services/Cancer-information-and-support/LocationSearch/320>

**Initial Treatment of Classical HCL**

The purine nucleoside analogues (PAs), pentostatin and cladribine, remain the standard front-line treatment for HCL(28), with overall response (OR) 90-100% (complete response (CR) in 70-90%), and no significant difference between the two agents. Remissions are durable (median 15 years), (5, 29), and survival is close to that for an age-matched general population. A small number of asymptomatic patients with well-preserved blood counts may not need immediate therapy. In patients presenting with infection, this should be treated before commencing PA therapy.

Pentostatin is administered as a short intravenous (IV) infusion every 2-3 weeks until a remission is achieved (usually 8-10 injections). The dose may need to be modified based on renal function. Patients can experience nausea for up to 72 hours after the infusion.

Cladribine (CDA) can be administered in a number of ways including as a 7- day continuous IV infusion (which may require a hospital admission), daily or weekly IV infusions or as a subcutaneous (SC) injection. There is no evidence that these are not all equally effective (30-32) and the preferred choice is usually 5 consecutive days SC administration, for convenience of delivery.

Both pentostatin and cladribine cause temporary myelosuppression, and a more prolonged immunosuppression. GCSF and prophylactic anti-infective agents (cotrimoxazole, aciclovir) may be initiated during treatment and continued for up to six months, or until adequate neutrophil and lymphocyte recovery. In the case of CDA, they should be commenced after the 5-day course of treatment, since rashes can occur when the drugs are given concurrently. Allopurinol is not required. Blood transfusion after purine analogue therapy should be with irradiated blood, indefinitely (33).

Splenectomy is rarely undertaken now, since PA therapy is effective in reducing the size of the spleen.

Interferon is now rarely used, being poorly tolerated and less effective than PAs, but may occasionally still be useful in patients who present with serious infection and severe pancytopenia.

Rituximab monotherapy has not been formally tested in the first- line setting but, based on the relatively low response rates seen in relapsed HCL (34), would not be recommended as an alternative to PA other than in special circumstances: Its use is reserved for patients unable to tolerate PAs, or who present with an active infection. There is evidence that improved remissions may be achieved with the combination of rituximab and a PA (35-38). A recent publication comparing concurrent versus delayed rituximab (by ≥ 6 months after detection of MRD in blood), showed MRD-free complete remission to be greatly enhanced by concurrent Rituximab(39). Concurrent Cladribine and Rituximab (CDAR) resulted in increased transient grade 3-4 thrombocytopenia, but higher neutrophil counts and platelet counts at 4 weeks, compared to delayed Rituximab.

**Assessment of Response**

Response assessment will normally include bone marrow trephine biopsy, which should be deferred for at least 4-6 months after cladribine therapy (8). CR is defined as the absence of hairy cells from the peripheral blood and bone marrow, along with resolution of organomegaly and cytopenias. Partial response (PR) is defined as a normalisation of cytopenias, along with a minimum 50% improvement in both organomegaly and bone marrow infiltration, with no circulating hairy cells. With pentostatin, the practice has been to perform bone marrow trephine biopsy after 8-9 injections, or when the blood count has normalised (apart from lymphopenia), offering 2-3 further pentostatin injections if CR is demonstrated (5).

In response assessment, CD20 staining in conjunction with morphological assessment is recommended, with use of DBA44 to identify subtle residual infiltration. Use of CD11c and annexin A1 is not recommended, these being expressed in myeloid cells, and use of CD79a and CD19 can over estimate residual disease, by staining of plasma cells(40). In CR, immunohistochemistry reveals no clustering (≥3 cells) of CD20‐positive or DBA44‐positive cells.

If there is PR, with significant residual HCL, a second course of cladribine may be required to achieve CR, usually given at least 6 months after the end of therapy. In a single centre follow‐up study of 242 patients(41), 18 patients treated with cladribine (12 as first‐line and six as second‐line therapy) who remained in PR after bone marrow reassessment, received a repeat treatment with cladribine 4–7 months after initial treatment, leading to CR in 14 patients, of whom all but one remained in CR at a median follow‐up of 6 years.

**Treatment of Relapsed or Refractory Classical HCL**

Despite the durable remissions achieved with front-line therapy, approximately 50% of patients will relapse. Younger patients (<40 years) may have shorter remissions (median 63 months vs 145 months for >40 years age) (42).

In the relapse setting PAs induce lower CR rates and shorter remissions than when used in frontline therapy (5). Addition of rituximab (6-8 doses given concurrently or sequentially) to a PA can improve this response but there is limited data on optimum schedule(43, 44). A poor response (remission lasting <3 years) or primary resistance to one PA may be overcome by switching treatment to the alternative PA(45).

Bendamustine plus rituximab has been used in a small study (12 patients) of relapsed HCL with promising results (100% OR, 60% CR) (46).

Moxetumumab pasudotox is a recombinant immunotoxin directed against CD22 and linked to a truncated *Pseudomonas exotoxin.* CD22 is strongly expressed on hairy cells. Initial studies showed promising results (OR 86%) in heavily pre-treated patients with relapsed/refractory HCL(47). In the pivotal international phase 2 trial, durable CRs were seen in 30% of patients with relapsed HCL, with bone marrow minimal residual disease (MRD) eradication in 85% of responding patients(48). Administration is by IV infusion on days 1, 3 and 5 of each 28-day cycle. Very little myelo- or immunosuppression is seen, but there is a risk of haemolytic uraemic syndrome (HUS) and/ or capillary leak syndrome (CLS). The latter are reversible and can be minimized by good pre-hydration.

**Experimental Approaches and Clinical Trials**

HCL is a rare disease, and it is important for patients with relapsed or refractory disease, to be considered for a clinical trial, particularly those who may benefit from a novel agent.

BRAF-MEK-ERK pathway inhibitors as monotherapy or in combination

Identification of the *BRAF* V600E mutation and a constitutively active BRAF‐MEK‐ERK pathway in HCL cells provided the scientific basis for therapeutic use of *BRAF* inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (trametinib) in patients with relapsed or refractory HCL (4).

After the first clinical description of a patient with HCL successfully treated with vemurafenib, two separate multicentre phase 2 clinical trials (US and Italian) were performed using vemurafenib in relapsed/refractory HCL (49). The drug was administered at a dose of 960 mg twice daily for a median of 16 weeks in the Italian cohort and 18 weeks in the US cohort (49). Overall response rate (ORR) was 96% (CR=35%) in the Italian trial (n=25 patients) and 100% (CR=42%) in the US cohort (n=24 patients). At a median follow‐up of 23 months, median treatment‐free survival in the Italian cohort was 25 months in patients who had achieved CR (18 months for those achieving PR); In the US study, the progression‐free survival and the overall survival at 1 year were 73% and 91%, respectively.

Efficacy and toxicity of vemurafenib was also investigated in 21 consecutive HCL patients treated on compassionate schemes outside clinical trials, with individual dosing regimens (240-1920 mg/d; median treatment duration, 90 days) (50). Responses were observed in all patients, with CR in 40% and median event-free survival 17 months. Although numbers were too small for adequately powered analyses, vemurafenib at 480 mg/day completely abrogated ERK phosphorylation of hairy cells *in vivo,* and response rates and kinetics appeared independent of vemurafenib dosing.

Vemurafenib is generally well tolerated, with adverse drug reactions (AEs) reversible and mostly grade 1‐2, with minimal myelotoxicity. AEs involve skin (rash, photosensitivity, palmar/plantar fibrosis, and warts) and joints (arthralgia, arthritis). Arthralgias usually respond to low dose corticosteroids. Skin tumours (basal cell carcinoma and squamous cell carcinomas) occur in ~9% patients (49). Dose reduction approaches have been used in more than 50% patients to limit side effects (49), although the benefit of dose reduction remains unclear, with similar side effects recorded at lower doses (50).

Another *BRAF* inhibitor, dabrafenib, has been given in combination with the MEK inhibitor, trametinib, to 43 relapsed/refractory HCL patients in an ongoing phase 2 multicentre trial. After a median of 17 months duration of treatment, ORR was 78% ( 49% CR) (51), suggesting no remarkable differences from vemurafenib monotherapy.

Vemurafenib is also under investigation in combination with rituximab in an ongoing phase 2 single centre trial for patients with relapsed/refractory disease (52) with vemurafenib (960 mg twice daily orally) given for 8 weeks, with rituximab (375 mg/m2 intravenously) every 2 weeks for 12 weeks. Interim analysis of 25 evaluable cases, showed CR 100%, with MRD‐negative CRs 61%. Toxicity was mostly grade 1‐2, and similar to that when either drug was used alone. This combination has shown no myelotoxicity.

Ibrutinib

B-cell receptor (BCR) signalling is functional in HCL (53), and the BCR pathway-associated Bruton’s tyrosine kinase inhibitor (BTKi), ibrutinib, inhibits survival and proliferation of hairy cells *in vitro* (54). In a phase 2 trial of 17 cases of relapsed/refractory HCL, ORR was 60% (25% CR and 35% PR) after prolonged administration of the drug (55). Individual case reports of ibrutinib in patients with HCL-V show promising effects and warrant further investigation (56, 57)

**Treatment of HCL Variant**

There is very little specific data on the treatment of HCL-V, but it is well recognised that the response rates and duration of response to PAs is inferior to that seen in classical HCL. For this reason it is recommended that cladribine plus rituximab be used as first- line therapy, based on small published series showing improvement in outcome with the combination(36, 58). Small numbers of patients with HCL-V have been treated with moxetumumab pasudotox with less good results than seen in classical HCL, but this may be attributable to the presence of bulky disease. Similarly, a minority of HCL-V patients have been treated on the ibrutinib Phase II trial, with the same outcome as the classical HCL cases. Clearly, BRAF inhibition is not appropriate, given that the variant cases do not harbour *BRAF* mutations. However *MAP2K* mutations are seen in about half the cases, and trametinib has been shown to have activity. Splenectomy may be considered in refractory cases to alleviate symptoms and cytopenias.

**Summary and Recommendations**

HCL is an uncommon chronic leukaemia, but advances in treatment over the last two decades mean that many classical HCL patients can have a near normal life expectancy. Identification of *BRAF* V600E as key to the pathogenesis of classical HCL has resulted in advances in therapeutics, particularly for relapsed and refractory disease.

HCL-V, long regarded as different from classical HCL, is now identified as a distinct entity, and treatment of HCL-V remains an area of unmet need.

Patients with both classical and variant forms of HCL should be considered for clinical trials.

* **Key diagnostic tests in suspected HCL should include blood film, bone marrow aspirate and trephine biopsy morphology, with flow cytometric immunophenotyping and immunohistochemistry. Consider CT of neck, thorax, abdomen and pelvis (grade 1A).**
* **Key differential diagnosis of classical HCL includes HCL-V, SDRPL, SMZL. Use history, examination and diagnostic tests to differentiate between them (grade 1A)**
* **Initial treatment of classical HCL in most patients should be with a purine analogue, cladribine or pentostatin (grade 1A). Interferon and splenectomy may have a role in selected patients (grade 2B).**
* **Response assessment, by bone marrow trephine biopsy, should be deferred until 4-6 months after initial therapy, with use of selected immunohistochemical stains to confirm CR (grade 2B).**
* **Options in relapsed disease include: purine analogue plus rituximab, moxetumumab pasudotox (grade 1A). In the UK, a license for moxetumub is expected in late 2020, with approval for use in patients receiving at least one prior PA and Rituximab, placing it as third line therapy.**
* **Experimental therapies e.g *BRAF* inhibition (vemurafenib), BTKi can be considered in relapsed, refractory disease, where there is evidence of *BRAF* mutation (grade 2B).**
* **Attention should be given to antibiotic and antiviral prophylaxis (grade 1B) and irradiated blood products are required after PA therapy (grade 1A).**
* **Cladribine plus rituximab is recommended as first line therapy for**

**HCL-V, based on small published series showing improvement in outcome with the combination (grade 1C).**

* **Patients with HCL-V or with relapsed classical HCL should be entered into clinical trials, if possible.**

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**Declaration of Interests**

The BSH paid the expenses incurred during the writing of this guidance.

All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. NPJ has received speaker fees from Roche, and educational grant and accommodation expenses from AbbVie. FF has received speaker fees from AbbVie, Janssen-Cilag; travel, accommodations or expenses from AbbVie, Janssen-Cilag; honoraria (panel review boards and independent advisor) from AbbVie, Menarini, Roche and research grants from Gilead. CD has been on advisory board for medimmune (now innate pharma) advisory boards for Roche. AJ has no conflicts of interest to declare.

**Review Process**

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (https://b-s-h.org.uk/guidelines/)

**Disclaimer**

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

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