**Vaccinations Recommended for Patients with Chronic Lymphocytic Leukaemia (CLL) and monoclonal B-cell lymphocytosis (MBL)**

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| 1  2 | 21/09/16  12/03/18 | Sections 2 and 9 on Hib vaccine revised; Section 3 meningococcal guidance clarified. Section 4 tetanus booster criteria revised and ‘Repevax’ changed to ‘Revaxis’. Section 6 advice on a 2nd dose of influenza vaccine clarified. Consultation summary revised. Vaccination schedule added as an appendix. | September 2018  March 2021 |
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1. **Introduction**

**Purpose**

Patients with chronic lymphocytic leukaemia (CLL) are at increased risk of a number of bacterial infections, including those caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa* and enteric Gram-negative bacilli (Itala *et al.* 1992, Whitaker *et al.* 2014).

There is no evidence that the rate and/or severity of viral infections with respiratory viruses such as influenza is greater than that of control populations, although it is accepted practice to vaccinate such patients against influenza (Whitaker *et al*. 2014, Sinisalo *et al.* 2003, Green Book Chapter 7).

Patients diagnosed with monoclonal B-cell lymphocytosis (MBL) are at approximately three-fold higher risk of hospitalisation with infection compared with a control population, and at a similar risk to patients with CLL (Moreira *et al.* 2013).

It was previously accepted that the predisposition to infection was mediated by immunoglobulin (Ig) deficiency. However, recent studies have shown that MBL/CLL patients are at increased risk of infection even if they have normal immunoglobulin levels (Moreira *et al.* 2013).

There are at least three guidelines in existence which are relevant to immunisation in CLL:

* British Committee for Standards in Haematology (Oscier *et al.* 2012)
* Infectious Diseases Society of America (Rubin *et al.* 2013)
* CDC Advisory Committee on Immunization Practices (Bennett *et al.* 2012).

These are referred to throughout this document as the BCSH, IDSA and ACIP guideline respectively.

The BCSH guideline states that there are no randomized studies showing that vaccination of any type alters infection rates or outcomes from acquired infections in CLL patients. However, it makes the following recommendations, all at B2 level (B = moderate quality of evidence, 2 = weak recommendation):

* Vaccination against *Streptococcus pneumoniae* (using a conjugate vaccine) and *Haemophilus influenzae* type B (Hib) is recommended at diagnosis. Patients who respond to vaccination and subsequently develop recurrent bacterial infections should be revaccinated if *S. pneumoniae* and Hib antibody levels have fallen.
* Annual vaccination against seasonal influenza and novel strains is recommended.
* Live vaccines such as polio, H. zoster and yellow fever should be avoided.
* Vaccinations should be avoided, if possible, 2 weeks prior to, during or up to 6 months after chemo-immunotherapy.

The IDSA guideline covers the whole area of vaccination of the immunocompromised host and makes no distinction between acute and chronic leukaemias. The ACIP guideline refers to pneumococcal vaccination only, and again makes no distinction made between acute and chronic leukaemias.

A number of relevant papers have been published on this topic. Whitaker *et al.* (2014) provides a scientific background to immunisation in monoclonal B-Cell lymphocytosis and CLL (which it considers as a single entity). It provides a summary of vaccination recommendations, which are based on a synthesis of literature review together with the IDSA and ACIP guidelines. Because it draws on IDSA it advises vaccination against meningococcus, diphtheria, pertussis and tetanus, none of which are mentioned in the BCSH guidelines.

*Pneumococcus*

The immunogenicity of the pneumococcal vaccines is complex. For instance, Sinsialo *et al.* (2003) cite evidence to suggest that polysaccharide vaccines are ineffective in CLL, as measured by the generation of an antibody response. However, Whitaker *et al.* (2014) report that patients who receive PPV23 followed by PCV13 have decreased antibody responses compared with those who receive the vaccines in the opposite order, suggesting that that PCV13 augments the immune response to a subsequent dose of PPV23.

The Green Book (chapter 25) recommends that children and adults with acute and chronic leukaemia should be offered a single dose of PCV13 followed by PPV23 at least two months later, irrespective of their routine childhood vaccinations. In chapter 25 it notes that antibody levels in patients vaccinated with PPV23 who have absent or dysfunctional spleen or chronic kidney disease decline rapidly, so such patients should be re-vaccinated every five years. However, it does not extend this recommendation to patients with leukaemia.

The ACIP guideline makes the same recommendation, but it also recommends a booster dose of PPV23 every five years thereafter. This applies to patients whether or not they have received PPV23 before, but if they have, the first dose of PCV13 should not be given until a year after the last dose of PPV23.

*Haemophilus influenzae* type B (Hib)

The BCSH guidance recommends Hib vaccination. The IDSA guideline recommends Hib vaccination, but only if the patient is ‘not current with recommendations for dose(s) of vaccine for immunocompetent persons in risk and age categories’ (this recommendation is interpreted to mean that patients who have already received the expected vaccinations for their age group do not need any additional vaccines).

All Hib vaccine available in the UK is combined with other vaccines, as either the “5-in-one” diphtheria/tetanus/acellular pertussis/inactivated polio vaccine/*H. influenzae* type b (DTaP/IPV/Hib) vaccine, or Hib/MenC conjugate.

Green Book (chapter 16) recommendations on administration relate mainly to children, and are difficult to apply to adults:

For children over one year of age and under ten years of age who have either not been immunised or not completed a primary course of diphtheria, tetanus, pertussis or polio, DTaP/IPV/Hib vaccination should be used. Children over one year and under ten years of age who have completed a primary course of diphtheria, tetanus, pertussis or polio should have Hib/MenC.

Individuals with immunosuppression and HIV infection (regardless of CD4 count) should be given Hib-containing vaccines in accordance with the recommendations above. These individuals may not make a full antibody response. Re-immunisation should be considered after treatment is finished and recovery has occurred. Specialist advice may be required.

Adults should therefore be vaccinated against Hib.

*Meningococcus*

The BCSH guideline makes no recommendation on meningococcal vaccination. The IDSA guideline recommends meningococcal conjugate vaccine only if the patient is ‘not current with recommendations for dose(s) of vaccine for immunocompetent persons in risk and age categories.’ The Green Book (chapter 7) makes special recommendations for patients with asplenia, splenic dysfunction and complement deficiency but not CLL. For individuals with ‘immunosuppression’ it recommends meningococcal vaccination in accordance with the routine schedule. It does not appear, therefore, that meningococcal vaccination (over and above ‘routine’ meningococcal vaccination) is indicated for CLL patients.

*Influenza*

The Green Book (chapter 7) recommends influenza vaccination for people who are immunosuppressed and the IDSA guideline recommends annual vaccination for patients with haematological malignancy. The live vaccine must not be used. De Lavallade *et al.* (2011) found that protective antibody responses were 85% in CLL patients who received one dose of flu vaccine and 95% in those who received two doses, 21 days apart. Based on this research, the BCSH guideline recommends that two doses of flu vaccine should be given to patients with CLL.

*Tetanus*

Neither the BCSH nor the IDSA guideline make any recommendations for tetanus immunisation. The Green Book (chapter 30) states that patients who are immunosuppressed may not be adequately protected against tetanus even if they are fully immunised, and should therefore be managed as if they were incompletely immunised (see p379 and Table 30.1). Whitaker *et al.* (2014) recommend a booster dose of tetanus at diagnosis and every 10 years thereafter.

*Other infections*

Immunisation against diphtheria, polio and pertussis is not mentioned in the BCSH guideline but is recommended by IDSA and Whitaker *et al.* (2014) The IDSA recommends that a combined DPT vaccine should be given to patients who are ‘not current with recommendations for dose(s) of vaccine for immunocompetent persons in risk and age categories.’ Thus, if a person is diagnosed with CLL who has not undergone the immunisation schedule that would be recommended for the same person if they did not have CLL, they should be vaccinated.

*Timing of vaccination*

The Green Book (chapter 7) says:

For individuals due to commence immunosuppressive treatments, inactivated vaccines should ideally be administered at least two weeks before commencement. In some cases this will not be possible and therefore vaccination may be carried out at any time and re-immunisation considered after treatment is finished and recovery has occurred.

The Green Book (chapter 25) says:

For leukaemia patients, PCV13 should be given from six months after completion of chemotherapy, and for bone marrow transplant patients, PCV13 should be offered 9-12 months following transplantation.

CLL is a chronic illness and it is unlikely that chemotherapy will be required within two weeks of diagnosis. This paragraph, therefore, is more likely to apply to acute rather than chronic leukaemia.

The IDSA guideline says that PCV13 should be administered to newly-diagnosed adults with leukaemia, and PPSV23 (=PPV23) at least eight weeks later. With respect to Hib, the IDSA guideline recommends vaccination ≥ 3 months after chemotherapy (and ≥6 months after anti–B-cell antibodies). This recommendation, however, seems to be based on an assumption that chemotherapy will be initiated soon after diagnosis of leukaemia (therefore presumably it is referring to acute leukaemias).

*Testing antibody levels*

The Green Book recommends against antibody testing before giving booster doses of PPV23 and does not recommend testing before giving a booster dose of tetanus vaccine (Green Book chapters 25 and 30).

The IDSA and ACIP guidelines and Whitaker *et al.* (2014) do not recommend checking antibody levels, either before vaccination or to confirm effective vaccination.

The BCSH guidance says:

Patients who respond to vaccination and subsequently develop recurrent bacterial infections should be revaccinated if *S. pneumoniae* and Hib antibody levels have fallen.

This implies that antibody levels should be tested after vaccination if a patient develops infections with one or other of these organisms.

Post-vaccination antibody levels can be tested to assess vaccine response. Guidance on vaccination in combined variable immunodeficiency (a condition in which the spectrum of organisms causing infection is similar to CLL/MBL) cites protective vaccination criteria of 1 μg/mL for Hib and 0.15 IU/mL for tetanus (Bonilla F *et* al., 2016). Advice from the North Cumbria University Hospitals Virology & Immunology Department is that it would be appropriate to test these levels 4 weeks after vaccination and boost once if they do not reach these thresholds (Adrian Heaps, personal communication).

Post-vaccination protective antibody criteria for pneumococcus are not well established (Bonilla F *et* al., 2016). It has been suggested that very low antibody values and high values well above the proposed cut-off are both clinically informative (Adrian Heaps, personal communication). However, in the absence of readily interpretable post-vaccination antibody levels for pneumococcus, their measurement is not proposed in this guidance.

**Summary**

* The evidence base for recommending specific vaccine schedules for patients with CLL suffers from a lack of evidence about the baseline rate of infections compared with control patients and a lack of evidence of the effectiveness of offering immunisation.
* The organisms that cause infections in CLL are mostly organisms for which immunisation is not available.
* Patients diagnosed with CLL have a similar infection risk to those with MBL.
* There is an historical assumption that the main reason for CLL patients being predisposed to infection is antibody deficiency, which is not supported by recent evidence.
* Guidance on the spectrum of organisms that need to be vaccinated against and the specific vaccines that should be used is inconsistent.
* There is no clear case for testing pre-vaccination antibody levels and the evidence of post-vaccination testing is patchy.
* Monocomponent vaccines are not available for a number of the organisms against which vaccination may be recommended, such as Hib and tetanus.

The recommendations made in this guidance document are a pragmatic synthesis of the information and guidance that is currently available.

**Scope**

This guideline applies to all patients with CLL and MBL treated by staff employed by Harrogate and District NHS Foundation Trust (the “Trust”). It is also relevant guidance for local General Practitioners.

In the absence of alternative guidance it would be reasonable to apply the recommendations in this document to patients with other indolent lymphoproliferative conditions that cause immunoparesis (*e.g*. marginal zone lymphoma. However, there is no substantial evidence base for such practice.

There are separate HDFT guidelines available for patients with absent or dysfunctional spleen (available at <http://nww.hdft.nhs.uk/EasysiteWeb/getresource.axd?AssetID=53227&type=full&servicetype=Attachment>), to whom these recommendations should not be applied.

**Guidance**

**1. Pneumococcus**

* At diagnosis:
  + Patients with no previous pneumococcal vaccination: Single dose of PCV13 followed by a dose of PPV23 at least two months later.
  + Patients with history of previous PPV23 vaccination: Single dose of PCV13 at least one year after last dose of PPV23, followed by a dose of PPV23 at least two months later.
* All patients: Boost with PPV23 every five years
* See below for recommendations on post-vaccination antibody testing

**2. *Haemophilus influenzae* type B (Hib)**

* At diagnosis: Single dose of Hib/MenC if the patient has not received a Hib-containing vaccine within the past five years.
* Single booster dose if post-vaccination antibody level is non-protective (see below for recommendations on post-vaccination antibody testing)

**3.Meningococcus**

* If there is no record of 4CMenB or MenACWY conjugate vaccine, these should be offered. Otherwise there are no recommendations outside of routine vaccination and travel-associated vaccination as recommended in the Green Book chapter 22

**4. Tetanus**

* At diagnosis: Booster dose of vaccine (Revaxis Td/IPV) if not received in the last 10 years, with a further single booster dose if post-vaccination antibody level is non-protective (see below for recommendations on post-vaccination antibody testing)
* All patients: Boost with Revaxis Td/IPV every 10 years, with additional booster if the patient sustains a ‘clean’ wound that is sufficient to require medical attention.
* If patient sustains a tetanus-prone wound: Booster dose of Revaxis plus one dose of human tetanus immunoglobulin at a different site.

**5. Diphtheria, polio, pertussis**

* Patients should be up to date with immunisation against these organisms, but no additional vaccination or boosters are required. GPs should be asked to confirm that patients have received the appropriate vaccines for their age group.

**6. Influenza**

* Inactivated flu vaccine annually at the start of the flu vaccination season. There is some evidence that a second dose a month later provides an optimal serological response and this should be offered if possible.

**7. Shingles**

* Shingles vaccine (Zostavax), which contains live attenuated varicella zoster virus, is contraindicated in patients with acute and chronic leukaemia, and should therefore not be given in CLL (Green Book chapter 28a, Zostavax SPC).

**8. Timing of vaccination with chemotherapy**

* If patients are treated with chemotherapy, vaccines should be given either two weeks before or six months after chemotherapy. If there is a need for chemotherapy within two weeks of vaccination, the need for repeat vaccination after its completion will need to be considered.

**9. Pre- and post-vaccination antibody checking**

* There is no recommendation to check antibody levels routinely before giving any of the vaccinations.
* Antibody levels against Hib and tetanus should be tested 4 weeks after vaccination. If they are “non-protective” (Hib < 1 μg/mL, tetanus < 0.15 IU/mL) a single booster of the corresponding vaccine should be given with a re-test 4 weeks later. The re-test results are for information only; If they are low the patient will be considered to be a “non-responder” and no further booster is recommended.
* If CLL patients who have been vaccinated against *S. pneumoniae* or Hib develop infections with these organisms, specific antibody testing should be carried out in consultation with an immunologist (advice will need to be sought externally to the Trust). The results should be interpreted according to the criteria recommended by the testing laboratory. Note that most infections with *H. influenzae* are caused bystrains other than type b, the Hib vaccine does not protect against infections with these strains, and in non‑bacteraemic infections it is unlikely that the serotype will be known. Therefore, respiratory tract infections with untyped *H. influenzae* do not necessarily indicate vaccine failure or non‑response.

**consultation, approval and ratification process**

See appendix 1 for those consulted during the preparation of the current version. The guidelines will be approved by the Clinical Lead for Haematology and a Consultant Microbiologist, prior to approval by the Area Prescribing Committee.

**document control**

The guideline will be published on the intranet with a review date of 2 years. It will be reviewed earlier if national guidance changes. Printed copies are only valid on the day printed.

**dissemination and implementation**

The guideline will be disseminated to all relevant staff, including local General Practitioners

**Monitoring compliance and effectiveness**

Any clinical incidents will be detected via the incident reporting processes. Audit of compliance will be considered within the annual audit planning process.

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**Appendices**

**Appendix 1: Consultation Summary**

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| **Those listed opposite have been consulted and any comments/actions incorporated as appropriate.**  The author must ensure that relevant individuals/groups have been involved in consultation as required prior to this document being submitted for approval. | **List Groups and/or Individuals Consulted** |
| **Andy Rawstron, Cathy Burton and Victoria Martin, HMDS, Leeds Teaching Hospitals NHS Trust** |
| **Claire Hall, Consultant Haematologist, HDFT** |
| **Gururaj Arumugakani, Consultant Immunologist, LTHT** |
| **Lesley Wright, Clinical Nurse Specialist, Haematology, HDFT** |
| **Thalani Balasubramaniam, Consultant Haematologist, HDFT** |
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